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(54) **IMPROVED FORMULATION FOR TOPICAL NON-INVASIVE APPLICATION IN VIVO**

VERBESSERTE FORMULIERUNG ZUR TOPISCHEN, NICHTINVASIVEN ANWENDUNG IN VIVO

FORMULATION AMELIOREE POUR L'APPLICATION TOPIQUE NON INVASIVE IN VIVO

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(56) References cited:
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Description

[0001] The invention relates to formulations comprising molecular arrangements which, owing to penetrant adaptability, are capable of penetrating pores in a barrier, despite the fact that the average diameter of said pores is smaller than the average penetrant diameter. The penetrants can transport agents or else enable agent permeation through the pores after said penetrants have entered said pores. The invention especially relates to new additives to said formulations, such as consistency builders, anti-oxidants or microbicides. It further relates to the preparation and use of such formulations wherein the agent is selected from corticosteroids. Finally, it relates to a method for the preparation of all such formulations.

[0002] The efficacy of any drug action is a multiparameter function in which the instrinsic potency, the accumulation as well as the elimination kinetics of the drug all play a role. While the former is entirely determined by the chemical composition of the drug the latter two parameters are sensitive to the galenic characteristics of agent formulation and also depend on the site and rate of agent administration.

[0003] Choosing the right mode and kind of drug application is thus as important as finding the right agent - in medicine as well as in the pharmaceutical industry. For example, if an epicutaneously administered drug is incapable of getting into and/or across the skin barrier such a drug has no practical value even if it has a high intrinsic potency. The same is true for the drugs that get into the skin easily but are there eliminated too rapidly to fully develop the desired biological action. In either case an optimization of agent formulation may help. Devising an improved galenic formulation is also much faster and more inexpensive than the invention of the corresponding new chemical entity.

[0004] It is already known in the art that the addition of surfactants to a membrane built from an amphiphilic substance may modify the membrane's adaptability to the pores of a porous barrier. Moreover, it has already been suggested that this fact may be used to provide agent transport into and/or across the skin, by incorporating and/or associating the agent into/on miniature droplets surrounded by the corresponding membranes, of at least one or more layers of amphiphilic molecules or an amphiphilic carrier substance, and suspended in a suitable liquid medium. These formulations are based on self-optimizing agent carriers which can penetrate a porous barrier such as skin by the virtue of their extremely high adaptability to the pores. This is described in greater detail in our earlier applications EP 475 160 B1, PCT/EP96/04526, PCT/EP98/5539 and PCT/EP98/6750.

[0005] Although the above-cited prior art already teaches a formulation comprising highly adaptable topically administered agent carriers which are suitable to enable agent transport into and/or across barriers, such as the human skin, however, these formulations are still capable of optimization in specific galenic characteristics in order to enhance practicability in storage and use. This holds especially true where certain galenic characteristics such as formulation viskosity, chemical resistance to oxidative degradation and/or microbiological stability of the formulation are concerned.

[0006] To avoid a repeated treatment, e.g. in view of side-effects possibly evoked, and in order to achieve high local agent concentration, it is necessary to appropriately adjust the viscosity of the formulation as this goal will be reached by enlarging the application area and/or layer thickness of the applied formulation. Varying the viscosity of the formulation is thus an appropriate means to avoid a number of successive treatments or else to enable appropriately high agent concentrations.

[0007] Storage related problems most often arise through lack of chemical resistance of the formulation against oxidative degradation of its components. This will obviously not only be important during the storage of the formulation inside the vessel before the application, but also during the application on the application site, when the formulation is exposed to ambient oxygen. Any oxidative process involving formulation components may not only degrade carrier and agent molecules and therefore continuously destroy both carrier and agent properties, but may also even lead to the formation of free radicals which then will cause further chemical attack on carrier and agent molecules, and therefore lead to an accelerated degradation of the components in the formulation. Ensuring proper storage and use therefore always involves protection of the formulation against oxidative degradation of its components.

[0008] Another storage-related problem lies in the prevention of the formulation against affection with microbes, such as bacteria and fungi, as this may also lead to degradation of carrier components and associated agent. Microbiological affection will not only reduce or eliminate both penetration ability of the carrier and activity of the agent, but can moreover lead to severe side-effects during the application of the drug. Therefore the formulation should not only be prevented from microbiological affection during its storage before use of the formulation, but should also be kept without affection once the vessel has been broken for the purpose of the application of the drug.

[0009] Above mentioned problems relating to poor agent transport into and/or across the skin and further to galenic characteristics are quite common to many corticosteroidal dermatics. Mineralocorticoids and glucocorticoids (hereinafter collectively referred to by the more general term "corticosteroids") are contained in approximately one third of all dermatics which now may be sold over the counter. Corticosteroids are commonly used, for instance, for the topical treatment of inflammatory diseases, but also are widely used for systemic medication, especially in the treatment of allergy-based syndroms.

[0010] Administered doses between a few micrograms per square centimeter, for the most potent corticosteroidal

agents, and up to a milligram per square centimeter for the less powerful drugs hence are quite common. Supraceding this limit reduces the efficacy of the concentration-driven drug permeation into the skin below the therapeutically acceptable level; superceding such drug amounts may result in intolerable local, or even systemic, side effects or else is simply not achievable by means of the classical galenic formulations.

[0011] For example, by raising the epidermal drug concentration one can increase the rate of drug transfer into the skin; by creating a local drug depot the problem of too rapid agent elimination may be solved. However, using a highly concentrated drug solution on the skin incurs the danger of agent precipitation on the skin and the greater likeliness of undesired side-effects. High skin irritation potential of many depot formulations, for example, is a serious obstacle for the successful therapeutic application of such medications. One of the chief reasons for this is that the currently used skin ointments or creams typically contain at least 0.1% and sometimes up to 5% of active ingredient as well as, a relative great amount of skin permeation enhancers in order to fluidize, which means to "soften" the skin which are however also very harmful to the skin. This is especially true when such drugs are used repeatedly and/or highly concentrated which often results in severe side effects, such as skin atrophy, which then enforces discontinuation of the therapy. Classical galenic formulations thus are generally lacking in potency and duration of biological functions if undesired severe side-effects evoked by a repeated treatment necessary to obtain sufficient agent concentration are to be avoided.

[0012] In view of the difficulties and problems cited hereinabove it would be desirable to have a formulation based on highly adaptable agent carriers which is more potent and can exert its desired biological function longer than similar drugs in the classical lotion or cream form, whereas severe side effects evoked by a repeated treatment can be reduced or even eliminated. It moreover is desirable to have a formulation based on highly adaptable agent carriers able to transport corticosteroidal agents into and/or across the skin wherein the viscosity of the formulation can be adjusted to enable enlarged application area and/or layer thickness, in order to avoid repetition in the treatment. It would also be very desirable if this formulation could be prevented from oxidative degradation and microbiological affection during its storage and use.

[0013] The present invention therefore aims at the solution of the above discussed problems. It especially addresses the problems with regard to storage and use of the specially optimized, highly adaptable agent carriers.

[0014] It is a further object of the present invention to overcome deficiencies of the prior art in delivering corticosteroidal formulations with regard to a well controlled trans- and/or intra-cutaneous transport of such drugs. Corticosteroidal formulations moreover are to be adjusted in viscosity, and prevented from oxidative degradation and microbiological affection.

[0015] Another object of the present invention is to provide a method for the preparation of such formulations for non-invasive applications.

[0016] Solutions to these objects in accordance with present invention are defined in the attached independent claims.

[0017] Convenient solutions with special properties are provided by the subject-matters of the subclaims.

[0018] As mentioned above the preparation and use of a formulation based on highly adaptable agent carriers have already been described. From this prior art, it is already generally known to add consistency builders and anti-oxidants to some such formulations, (cf. e.g. PCT/EP96/04526; Claim 18). However, this teaching is a general rule without any practical value, as it obviously lacks any specification for the use. This holds especially true, for instance, for the addition of a consistency builder which enables the formulation to be adjusted to the intended dose of the drug. This addition can obviously not be effected by a simple trial-and-error procedure, or accidentally, by the skilled person, since final drug action is essentially concerned. It is moreover essentiell to appropriately select type and amount of the added anti-oxidant or microbicide, as this obviously affects storage and use of the formulation.

[0019] It is known from prior art to use corticosteroids as the agent associated with highly adaptable agent carriers (cf. PCT/EP96/04526; Claim 15; PCT/EP91/01596 Examples 173-175). But, as for said additives; this disclosure provides no more than a general rule, to add said agent to said agent carriers without any further specification, as is however considered essentiell for the application of the'dntg. Consequently said prior art only generally teaches the use of corticosteroids as a test agent for the evaluation of pore penetration rate, rather than teaching the preparation of a usable dermatics product based on highly adaptable agent carriers containing corticosteroids. This is indicated by the total amount of hydrocortisone which is to be incorporated in the highly adaptable carrier (examples 173-175 of PCT/EP91/01596: 10 Mikrograms per about 100 mg dry weight of agent carrier). The very low relative proportion of about 0,1 per mille of hydrocortisone based on the total dry weight of formulation is far away from any therapeutically useful drug concentration and also far away from any corticosteroid concentration given in this application.

[0020] Moreover , the prior art does not teach, how the specific application of corticosteroids is to be effected if, more systemic or else more topical drug action is to be achieved. It therefore is necessary to separately adress the problem of both systemic and non-systemic drug action of applied corticosteroidal dermatics based on the highly adaptable agent carriers, as it is done in this application.

[0021] Furthermore, in general, both topical non-systemic administration, and substantially systemic administration

of corticosteroidal dermatics is accompanied by the problem that the more gentle acting agents, like hydrocortisone, only exhibit a rather short and week activity, whereas the more recently developped related agents, such as prednicarbat- or triamcinolone-derivatives are more potent and also act longer, but are also more harmful to the body, as they can evoke severe side-effects if they are applied highly concentrated and/or repeatedly.

[0022] In contrast to this, topical corticosteroid delivery mediated by highly adaptable agent carriers can be varied systematically whereby severe side-effects are dramatically reduced or even avoided. Depending on the precise application conditions and carrier design, between 100% and less than 5% of the locally administered drug can be deposited into the outermost skin region. Low area-dose favors drug retention in the skin, while larger amounts of a drug shift the distribution towards systemic circulation. It is possible to reach therapeutically meaningful drug concentrations in the blood after a single epicutaneous administration of corticosteroids by said carriers, while one can also keep blood level below a few per cent.

[0023] Unexpectedly, employment of such highly adaptable agent carriers together with an agent selected from corticosteroids provides biologically efficient product at unprecedent small doses per area. As is shown further below, all tested corticosteroids thus gained in potency (by the factor of 2 to 10) and in duration of action (by up to 5-fold) when they were administered on the intact skin by means of highly adaptable agent carriers. In contrast to prior art, ointments and creams containing corticosteroids, minute amounts of corticosteroids in highly adaptable agent carriers, consequently, suffice for good biological drug action.

[0024] Generally, material abrasion from the surface shortens the therapeutic effect in a conventional cream or lotion. It is another advantage of the present invention that such problems are not obversed with the formulations based on highly adaptable agent carriers which thus exert a much longer biological action than standard correponding medications. This is due to the fact that such highly adaptable agent carriers generate a drug depot in the viable skin portions, rather than on the skin surface. It is a characteristic feature of the present invention, that a formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, provided that the penetrants can transport agents or else enable agent permeation through the pores after penetrants have entered pores, the agents associated with said penetrants being corticosteroids, especially glucocorticoids or mineralocorticosteroids, has a relative content of corticosteroids of above 0.1 weight-%, relative to total dry mass of the formulation, and that the formulation comprises at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100 % per 6 months.

[0025] It is preferred that the formulation further comprises at least one consistency builder in an amount that increases the formulation viscosity above that of the non-thickened corresponding formulation to maximally 5 Ns/m^2 so that spreading over, and retention at, the application area is enabled and/or at least one microbicide in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days.

[0026] It is thus possible to prolong storage and use of the formulation and to advantageously increase practicability of the formulation.

[0027] It then is preferred if said at least one consistency buildner is added in an amount that increases the formulation viscosity to up to 1 Ns/m^2 and more preferably to up to 0.2 Ns/m^2.

[0028] It also is preferred if said at least one antioxidant is added in an amount that reduces the increase of oxidation index to less than 100 % per 12 months and more preferably to less than 50 % per 12 months.

[0029] For a formulation comprising soy bean phosphatidylcholine as the main degrading species, the increase of the oxidation index is reduced to less than 0.45 units, preferably to less than 0.22 units and even more preferably to less than 0.1 units, per 12 month.

[0030] In preferred embodiments of the invention said at least one microbicide is added in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 3 days, and more preferably after a period of 1 day.

[0031] It is preferred if that anti-oxidant is selected from synthetic phenolic antioxidants, such as butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX, etc.), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ); aromatic amines (diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol, tetrahydroindenoindol); phenols and phenolic acids (guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid , salicylic acid, nordihydroguaiaretic acid (NDGA), eugenol); tocopherols (including tocopherols (alpha, beta, gamma, delta) and their derivatives, such as tocopheryl-acylate (e.g. - acetate, -laurate, myristate, -palmitate, -oleate,-linoleate, etc., or an y other suitable tocopheryl-lipoate), tocopheryl-POE-succinate; trolox and corresponding amide and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters (e.g. 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid, etc.). It may also be advantageous to use various drugs interfering with oxidation,

including but not limited to non-steroidal anti-inflammatory agents (NSAIDs, such as indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminephen); aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics (amiodarone, aprindine, asocainol), ambroxol, tamoxifene, b-hydroxytamoxifene; calcium antagonists (nifedipine, nisoldipine, nimodipine, nicardipine, nilvadipine), beta-receptor blockers (atenolol, propranolol, nebivolol); also useful are the preferentially oxidised compounds, such as sodium bisulphite, sodium metabisulphite, thiourea; chellating agents, such as EDTA, GDTA, desferral; miscellaneous endogenous defence systems, such as transferrin, lactoferrin, ferritin, cearuloplasmin, haptoglobion, heamopexin, albumin, glucose, ubiquinol-10); enzymatic antioxidants, such as superoxide dismutase and metal complexes with a similar activity, including catalase, glutathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids (flavones, flavonols, flavonones, flavanonals, chacones, anthocyanins), N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamatic acids and their esters (coumaric acids and esters, caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid, sinapic acid); spice extracts (e.g. from clove, cinnamon, sage, rosemary, mace, oregano, allspice, nutmeg); camosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives (e.g. U74006F); tryptophan metabolites (e.g. 3-hydroxykynurenine, 3-hydroxyanthranilic acid), and organochalcogenides.

[0032] Especially, a preferred concentration of BHA or BHT is between 0.001 and 2 w-%, more preferably is between 0.0025 and 0.2 w-%, and most preferably is between 0.005 and 0.02 w-%, of TBHQ and PG is between 0.001 and 2 w-%, more preferably is between 0.005 and 0.2 w-%, and most preferably is between 0.01 and 0.02 w-%, of tocopherols is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.075 w-%, of ascorbic acid esters is between 0.001 and 5, more preferably is between 0.005 and 0.5, and most preferably is between 0.01 and 0.15 w-%, of ascorbic acid is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.1 w-%, of sodium bisulphite or sodium metabisulphite is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01-0.15 w-%, of thiourea is between 0.0001 and 2 w-%, more preferably is between 0.0005 and 0.2, and most preferably is between 0.001-0.01 w-%, most typically 0.005 w-%, of cysteine is between 0.01 and 5, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1 and 1.0 w-%, most typically 0.5 w-%, of monothioglycerol is between 0.01 and 5 w-%, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1-1.0 w-%, most typically 0.5 w-%, of NDGA is between 0.0005-2 w-%, more preferably is between 0.001-0.2 w-%, and most preferably is between 0.005-0.02 w-%, most typically 0.01 w-%, of glutathione is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.2 w-%, most typically 0.1 w-%, of EDTA is between 0.001 and 5 w-%, even more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.2 w-%, most typically between 0.05 and 0.975 w-%, of citric acid is between 0.001 and 5 w-%, even more preferably is between 0.005 and 3 w-%, and most preferably is between 0.01-0.2, most typically between 0.3 and 2 w-%.

[0033] In preferred embodiments of the invention, the microbicide is selected from short chain alcohols, including ethyl and isopropyl alcohol, chlorbutanol, benzyl alcohol, chlorbenzyl alcohol, dichlorbenzylalcohol, hexachlorophene; phenolic compounds, such as cresol, 4-chloro-m-cresol, p-chloro-m-xylenol, dichlorophene, hexachlorophene, povidon-iodine; parabenes, especially alkyl-parabenes, such as methyl-, ethyl-, propyl-, or butyl- paraben, benzyl paraben; acids, such as sorbic acid, benzoic acid and their salts; quaternary ammonium compounds, such as alkonium salts, e.g. a bromide, benzalkonium salts, such as a chloride or a bromide, cetrimonium salts, e.g. a bromide, phenoalkecinium salts, such as phenododecinium bromide, cetylpyridinium chloride and other salts; furthermore, mercurial compounds, such as phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, or any antibiotically active compounds of biological origin, or any suitable mixture thereof.

[0034] In especially preferrred embodiments, the bulk concentration of short chain alcohols in the case of ethyl, propyl, butyl or benzyl alcohol preferably is up to 10 w%, more preferably is up to 5 w-%, and most preferably is in the range between 0.5-3 w-%, and the bulk concentration of chlorobutanol preferably is in the range between 0.3-0.6 w-%; furthermore, the preferred bulk concentration of parabenes is in the range between 0.05-0.2 w-%, in the case of methyl paraben, and is in the range between 0.002 - 0.02 w-%, in the case of propyl paraben; bulk concentration of sorbic acid preferably is in the range between 0.05-0.2 w-%, and in the case of benzoic acid preferably is in the range between-0.1-0.5w- %; bulk concentration of phenols, triclosan, is preferably in the range between 0.1-0.3 w-%, and bulk concentration of chlorhexidine preferably is in the range between 0.01-0.05 w-%.

[0035] It further is preferred if that consistency builder is selected from pharmaceutically acceptable hydrophilic polymers, such as partially etherified cellulose derivatives, comprising carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl- or methyl-cellulose; completely synthetic hydrophilic polymers comprising polyacrylates , polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate, polyacryloni-

trile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols, poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, (hydrazine cross-linked) hyaluronic acid, silicone; natural gums comprising alginates, carrageenan, guar-gum, gelatine, tragacanth, (amidated) pectin, xanthan, chitosan collagen, agarose; mixtures and further derivatives or co-polymers thereof and/or other pharmaceutically, or at least biologically, acceptable polymers. In especially, the polymer weight fractions preferably are in the range between 0.05 % and 10%, more preferably are in the range between 0.1% and 5 %, even more preferably are in the range between 0.25 % and 3.5 % and most preferably are in the range between 0.5 % and 2 %.

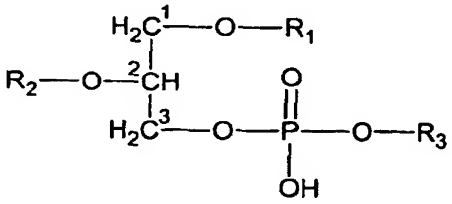
[0036] It has been found that viscosity is best suited if the consistency builder is added in an amount that increases the formulation viscosity above that of the non-thickened corresponding formulation, preferably to up to 1 Ns/m^2 and even more preferably to up to 0.2 Ns/m^2.

[0037] That corticosteroid is preferably selected from alclonetasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone, betamethasone 17-valerate, betamethasone 17,21-divalerate, betamethasone 21-acetate, betamethasone 21-buytrate, betamethasone 21-propionate, betamethasone 21-valerate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, cortexolone, corticosterone, cortisone, cortisone 17-acetate, 21-deoxybetamethasone, 21-deoxybetamethasone 17-propionate, deoxycorticosterone, desonide, desoxymethasone, dexamethasone, diflorasone diacetate, diflucortolone valerate, fluclorolone acetonide, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone , 9-alpha-fluorocortisone, 9-alpha-fluorohydrocortisone, 9-alpha-fluoroprednisolone, fluprednidene acetate, flurandrenolone, halcinonide, hydrocortisone, hydrocortisone 17-acetate, hydrocortisone 17-butyrate, hydrocortisone 17-propionate, hydro cortisone 17-valerate, hydrocortisone 21-acetate, hydrocortisone 2 1-butyrate, hydrocortisone 21-propionate, hydrocortisone 21-valerate, 17-alpha-hydroxyprogesterone, methylprednisolone acetate, mometasone furoate, prednisolone, prednisone, prednisone 17-acetate, prednisone 17-valerate, progesterone, triamcinolone, triamcinolone acetonide.

[0038] In a specific embodiment of the invention the penetrants are suspended or dispersed in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, provided that said at least two substances differ by at least a factor of 10 in solubility in said liquid or else that said substances when in the form of homo-aggregates, for the more soluble substance, or of hetero-aggregates, for any combination of both said substances, have a preferred average diameter smaller than the diameter of the homo-aggregates containing merely the less soluble substance; or else provided that the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating in the vicinity of thermal energy.

[0039] It then is preferred that the more soluble substance tends to solubilise the droplet and the content of such substance is up to 99 mol-% of solubilising concentration or else corresponds to up to 99 mol-% of the saturating concentration in the unsolubilised droplet, whichever is higher. It can be an advantage if the content of the more soluble substance is below 50 %, especially below 40 % and most preferably below 30 %, of the respective solubilising concentration of said substance. It also is often advantageous if the content of the more soluble substance is below 80 %, preferably below 65 % and most preferably below 50 % of the saturation concentration of said substance in the droplet.

[0040] In many highly preferred embodiments of the invention, the less soluble amongst the aggregating substances is a lipid or lipid-like material, especially a polar lipid, whereas the substance which is more soluble in the suspending liquid and which increases the droplet adaptability belongs to the class of surfactants or else has surfactant-like properties. A specific embodiment of the invention is prepared from a lipid or lipid-like material (which may be a lipid or a lipoid from a biological source or a corresponding synthetic lipid or any of its modifications), said lipid preferably belonging to the class of pure phospholipids corresponding to the general formula



where R_1 and R_2 is an aliphatic chain, typically a C_{10-20}-acyl, or -alkyl or partly unsaturated fatty acid residue, in particular an oleoyl-, palmitoeloyl-, elaidoyl-, linoleyl-, linolenyl-, linolenoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or stearoyl chain; and where R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_{1-4}-alkyl, C_{1-5}-

alkyl substituted with carboxy, C_{2-5}-alkyl substituted with hydroxy, C_{2-5}-alkyl substituted with carboxy and hydroxy, or C_{2-5}-alkyl substituted with carboxy and amino, inositol, sphingosine, or salts of said substances, said lipid comprising also glycerides, isoprenoid lipids, steroids, sterines or sterols, of sulphur- or carbohydrate-containing lipids, or any other bilayer forming lipids, in particular half-protonated fluid fatty acids. Preferably, said lipid is selected from the group comprising phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, phosphatidylserines, sphingomyelins and other sphingophospholipids, glycosphingolipids (including cerebrosides, ceramidepolyhexosides, sulphatides, sphingoplasmalogens), gangliosides and other glycolipids or synthetic lipids, in particular with corresponding sphingosine derivatives, or any other glycolipids, whereby two similar or different chains can be ester-groups-linked to the backbone (as in diacyl and dialkenoyl compound) or be attached to the backbone with ether bonds, as in dialkyl-lipids.

[0041] It is preferred if the surfactant or surfactant-like material is a nonionic, a zwitterionic, an anionic or a cationic surfactant, especially a fatty-acid or -alcohol, an alkyl-tri/di/methyl-ammonium salt, an alkylsulphate salt, a monovalent salt of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, etc., an acyl- or alkanoyl-dimethyl-aminoxide, esp. a dodecyl- dimethyl-aminoxide, an alkyl- or alkanoyl-N-methylglucamide, N-alkyl-N, N- dimethylglycine, 3-(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a polyethylene-glycol-octylphenyl ether, esp. a nonaethylene-glycol-octylphenyl ether, a polyethylene-acyl ether, esp. a nonaethylen-dodecyl ether, a polyethylene-glycol-isoacyl ether, esp. a octaethylene-glycol-isotridecyl ether, polyethylene-acyl ether, esp. octaethylenedodecyl ether, polyethylene-glycol-sorbitane-acyl ester, such as polyethylenglykol-20-monolaurate (Tween 20) or polyethylenglykol-20-sorbitan-monooleate (Tween 80), a polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene-lauryl, -myristoyl, -cetylstearyl, or -oleoyl ether, as in polyhydroxyethylene-4 or 6 or 8 or 10 or 12, etc., -lauryl ether (as in Brij series), or in the corresponding ester, e.g. of polyhydroxyethylen-8-stearate (Myrj 45), -laurate or -oleate type, or in polyethoxylated castor oil 40, a sorbitane-monoalkylate (e.g. in Arlacel or Span), esp. sorbitane-monolaurate, an acyl- or alkanoyl-N-methylglucamide, esp. in or decanoyl- or dodecanoyl-N-methylglucamide, an alkylsulphate (salt), e.g. in lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium glycodeoxycholate, sodium oleate, sodium taurate, a fatty acid salt, such as sodium elaidate, sodium linoleate, sodium laurate, a lysophospholipid, such as n-octadecylene(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-acyl-, e.g. lauryl or oleoyl-glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-tetradecyl- glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, a corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospholipid or a corresponding short-chain phospholipid, or else a surface-active polypeptide.

[0042] Penetration rate of agent carriers is often maximized if the average penetrant diameter is chosen to be between 30 nm and 500 nm, preferably between 40 nm and 250 nm, even more preferably between 50 nm and 200 nm and most preferably between 60 nm and 150 nm.

[0043] Pore penetration rate of agent carriers is often optimized in terms of the relative ratio between penetrant and pore size, if the average diameter of the penetrant is 2 to 25 times bigger than the average diameter of the pores in the barrier, preferably between 2.25 and 15 times bigger, even more preferably between 2.5 and 8 times bigger and most preferably between 3 and 6 times bigger than said average pore diameter.

[0044] Specific preferred embodiments of the invention are characterized by the fact, that the dry weight of all carrier droplets in a formulation for the use on human or animal skin is 0.01 weight-% (w-%) to 40 w-% of total formulation mass, in particular between 0.1 w-% and 30 w-%, particularly preferably between 0.5 w-% and 20 w-%, and most preferably between 1 w-% and 10 w-%.

[0045] If the formulation is to be applied on human or animal mucosa the dry weight of all carrier droplets in a formulation is advantageously chosen to be in the range between 0.0001 w-% and 30 w-% of total formulation mass.

[0046] For the preparation of a formulation it is preferred if the pH of the carrier suspension is between 4 and 10, preferably between 5 and 9, and even more often up to 8.5, as required in order to maximise the stability of formulation, depending on the pH of the carrier suspension.

[0047] A method for the preparation of a formulation for non-invasive application in vivo according to the invention comprises the use of at least one amphiphilic substance, at least one polar fluid, at least one edge-active substance or surfactant, at least one corticosteroid in an amount of more than 0.1 w-% based on total dry mass of the formulation and, in case, other customary ingredients, which together form said formulation.

[0048] It then is preferred if at least one edge-active substance or surfactant, at least one amphiphilic substance, at least one hydrophilic fluid and the agent are dissolved to form a solution and, if required, are mixed separately, the resulting (partial) mixtures or solutions then being combined to subsequently induce, preferably by action of mechanical energy, such as shaking, stirring, vibrating, homogenising, ultrasonication, shear, freezing and thawing, or filtration using convenient driving pressure, the formation of penetrants that associate with and/or incorporate the agent.

[0049] It is advantageous if said amphiphilic substances are either used as such, or dissolved in a physiologically compatible polar fluid, which may be water or miscible with water, or in a solvation-mediating agent, together with a polar solution.

[0050] It further is preferred that said amphiphilic substances are dissolved in highly volatile alcohols, especially

ethanol, or in other pharmaceutically acceptable organic solvents, which are then removed, esp. by evaporation, prior to making the final preparation.

[0051] It may also be advantageous if said polar solution contains at least one edge-active substance or surfactant.

[0052] For the preparation of a formulation according to the invention it further is preferred, that the formation of said penetrants is induced by the addition of the required substances into a fluid phase, evaporation from a reverse phase, by injection or dialysis, if necessary under the influence of mechanical stress, such as shaking, stirring, especially high velocity stirring, vibrating, homogenising, ultrasonication, shearing, freezing and thawing, or filtration using convenient, especially low (1 MPa) or intermediate (up to 10 MPa), driving pressure.

[0053] It then is convenient if the formation of said penetrants is induced by filtration, the filtering material having pores sizes between 0.01 μm and 0.8 μm, preferably between 0.02 μm and 0.3 μm, and most preferably between 0.05 μm and 0.15 μm, whereby several filters may be used sequentially or in parallel.

[0054] Furthermore, it is preferred if said agents and penetrants are made to associate, at least partly, after the formation of said penetrants, e.g. after injecting a solution of the drug in a pharmaceutically acceptable fluid, such as ethanol, 1-and 2-propanol, benzyl alcohol, propylene glycol, polyethylene glycol (molecular weight: 200 - 400 D) or glycerol into the suspending medium, said penetrants being formed previously, using the corresponding or some other suitable manufacturing method, or simultaneously with the drug injection, if required using a co-solution of the drug and, at least some, penetrant ingredients.

[0055] It may be advantageous if the penetrants, with which the agent molecules are associated and/or into which the agent molecules are incorporated, are prepared just before the application of the formulation, if convenient from a suitable concentrate or a lyophylisate.

[0056] It is preferred if the content of corticosteroids is between 0.1 relative weight % (rw-%) and 20 rw-%, more preferably between 0.25 rw-% and 10 rw-% and even more preferably between 0.5 rw-% and 5 rw-% with regard to total penetrant dry mass.

[0057] It then is preferred if said corticosteroid is triamcinolone or one of its derivatives, such as acetonide, the relative content thereof is below 2 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 1 w-% and most typically is below 0.5 w-%.

[0058] It also is preferred if the corticosteroid is hydrocortisone or one of its derivatives, the relative content thereof is below 20 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 12.5 w-% and most typically is below 5 w-%.

[0059] Further, it is preferred if said corticosteroid is dexamethasone or one of its derivatives, the relative content thereof is below 15 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 10 w-% and most typically is below 5 w-%.

[0060] It equally is preferred if said corticosteroid is clobetasol or one of its derivatives, such as propionate, the relative content thereof is below 15 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 10 w-% and most typically is below 5 w-%.

[0061] It is a preferred feature of the invention that the content of said corticosteroid is below the saturation maximum, defined as the point at which the corticosteroid begins to crystallise in or outside the carrier, such maximum depending on interactions between the amphiphilic molecules comprising the carrier and the agent molecules and frequently being reflected in the membrane/ or oil/water partition coefficient difference for the main carrier component and said corticosteroid or else relates to the mismatch in molecular size between the carrier and corticosteroid molecules, the drugs with a lower compatibility typically having lower saturation values.

[0062] It may be advantageous if in order to speed up drug action a permeation enhancer is added, which preferablyis selected from 1-acyl-azacycloheptan-2-ones (azones), 1-acyl-glucosides, 1-acyl-polyoxyethylenes, 1-acyl-saccharides, 2-n-acyl-cyclohexanones, 2-n-acyl-1,3-dioxolanes (SEPA), 1,2,3-triacyl-glycerols, 1-alkanols, 1-alkanoic acids, 1-alkyl-acetates, 1-alkyl-amines, 1-alkyl-n-alkyl-polyoxyethylenes, 1-alkyl-alkylates, n-alkyl-beta-D-thioglucosides, 1-alkyl-glycerides, 1-alkyl-propyleneglycols, l-alkyl-polyoxyethylenes, (1-alkyl-)2-pyrrolidones, alkyl-acetoacetates, alkylene-glycols, alkyl-methyl-sulphoxides (alkyl-DMSO), alkyl-propionates, alkyl-sulphates, diacyl-succinates, diacyl-N,N-dimethylaminoacetates (DDAA), diacyl-N,N-dimethylaminoisopropionates (DDAIP), phenyl-alkyl-amines.

[0063] This addition of permeation enhancers is not comparable to the addition of permeation enhancers as already effected in classical galenic preparations, such as ointments and lotions, as in the art, the permeation enhancers are solely added for the purpose of fluidization of the skin. In the present case the permeation enhancers are added to speed up drug action which is to speed up distribution between agent carrier and surroundings. This content of permeation enhancer is not suited to substantially fluidize skin in order to increase the pore penetration rate of agent carriers and therefore is inherently different from prior art.

[0064] It then is preferred if the bulk concentration range of the preferably used enhancers is up to and around 5 % for 1-capryl-propylene glycol, 6-10 % for 1-[2-(decylthio)ethyl] azacyclopentan-2-one (=HPE-101), < 10% for 1-dodecanol, < 10 % for 1-dodecyl-azacycloheptan-2-one (=azone), in the range of 10 % for 2-n-nonyl-1,3-dioxolane (SEPA), < 10 % for 2-n-octylcyclohexanone, up to, and preferably around, up to 20 % for DMSO, up to, and preferably between

5 % and 40 % for ethanol, in the range of 10 % or higher for ethylene glycol, up to 30 % for ethyl acetate, 5-50 % for glycerol, up to 75 % for isopropanol, 1-20 % for isopropyl myristate, between 1 and, preferably, 20 % for oleic acid and oleyl-alcohol, of the order of around 1 % for oleyl-polyoxyethylene-ether, at least 10 % for propylene glycol.

[0065] The caveat pertaining to these ranges is that the relative and absolute potency of various skin permeation enhancers differs, which makes absolute comparisons difficult. In principle, it is the concentration of an enhancer in the skin which determines the enhancement success. However, it is the nominal enhancer concentration on the skin which typically is considered or is quoted in the literature. The two values often differ by several orders of magnitude, are sensitive to drug-enhancer association, and also may vary with the application conditions. Too small enhancer reservoir on the surface, for example, in the case of a fast enhancer diffusion across the skin or evaporation, leads to substance depletion. It also changes the final system properties.

[0066] It is a preferred feature of the invention that said corticosteroid is added in an amount which enables the formulation to be applied corresponding to an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between 0. 1 mg cm^{-2} and 15 mg cm^{-2}, more preferably between 0.5 mg cm^{-2} and 10 mg cm^{-2}, particularly preferably between 0.75 mg cm^{-2} and 5 mg cm^{-2} and most preferably between 1 mg cm^{-2} and 2.5 mg cm^{-2}, if said corticosteroid is desired to exert a therapeutic effect in the deep subcutaneous, e.g. muscle or joints, tissue or else in the remote tissues, including the whole body.

[0067] It is another preferred feature of the invention that said corticosteroid is added in an amount which enables the formulation to be applied with an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between 1 μg cm^{-2} and 250 μg cm^{-2}, more preferably between 2.5 and 100 μg cm^{-2}, even more preferably between 5 μg cm^{-2} and 50 μg cm^{-2} and most preferably between 7.5 μg cm^{-2} and 20 μg cm^{-2}, if said corticosteroid is desired to exert a mainly local, that is, superficial, rather than systemic therapeutic effect.

[0068] It is preferred if consistency and, if necessary other characteristics of the formulation are appropriately selected to enable spraying, smearing, rolling or sponging of the formulation on the application area in particular by using a sprayer, spender, roller or sponge, as appropriate.

[0069] It is another preferred feature of the invention that for formulations according to the invention for the preparation of a medicament for the non-invasive application of corticosteroids the area dose, as expressed by the total dry mass of penetrant applied per unit area, is selected to be between 0.1 mg cm^{-2} and 15 mg cm^{-2}, preferably between 0.5 mg cm^{-2} and 10 mg cm^{-2}, particularly preferably between 0.75 mg cm^{-2} and 5 mg cm^{-2} and most preferably between 1 mg cm^{-2} and 2.5 mg cm^{-2}, if said corticosteroid is desired to exert a substantial therapeutic effect in the deep subcutaneous, e.g. muscle or joints, tissue or else in the remote tissues, including the whole body.

[0070] It otherwise is preferred if for formulations according to the invention for the preparation of a medicament for the non-invasive application of corticosteroids the area-dose, as expressed by the total dry mass of penetrants applied per unit area, is chosen to be between 1 μg cm^{-2} and 250 μg cm^{-2}, preferably between 2.5 μg cm^{-2} and 100 μg cm^{-2} , more preferably between 5 μg cm^{-2} and 50 μg cm^{-2} and most preferably between 7.5 μg cm^{-2} and 20 μg cm^{-2}, to achieve mainly local, that is, superficial, rather than systemic effect of the drug.

[0071] It may be advantageous for formulations for the preparation of a medicament for the non-invasive application of corticosteroids associated with or encapsulated into penetrants according to the invention if the application is effected by spraying, smearing, rolling or sponging on the application area in particular by using a sprayer, spender, roller or sponge, as appropriate.

[0072] A preferred use of a formulation in accordance with the invention is for the preparation of a medicament for the treatment of inflammatory disease, dermatosis, kidney or liver failure, adrenal insufficiency, aspiration syndrome, Behcet syndrome, bites and stings, blood disorders, such as cold-haemagglutinin disease, haemolytic anemia, hypereosinophilia, hypoplastic anemia, macroglobulinaemia, trombocytopenic purpura, furthermore, for the management of bone disorders, cerebral oedema, Cogan's syndrome, congenital adrenal hyperplasia, connective tissue disorders, such as lichen, lupus erythematosus, polymyalgia rheumatica, polymyositis and dermatomyositis, epilepsy, eye disorders, such as cataracts, Graves ophthalmopathy, haemangioma, herpes infections, neuropathies, retinal vasculitis, scleritis, for some gastro-intestinal disorders, such as inflammatory bowel disease, nausea and oesophageal damage, for hypercalcaemia, infections, e.g. of the eye (as in infections mononucleosis), for Kawasaki disease, myasthenia gravis, various pain syndromes, such as postherpetic neuralgia, for polyneuropathies, pancreatitis, in respiratory disorders, such as asthma, for the management of rheumatoid disease and osteoarthritis, rhinitis, sarcoidosis, skin diseases, such as alopecia, eczema, erythema multiforme, lichen, pemphigus and pemphigoid, psoriasis, pyoderma gangrenosum, urticaria, in case of thyroid and vascular disorders.

[0073] The following examples and results of in-vitro and in-vivo studies shown in attached figures should illustrate the scope of the invention without setting or delineating its limits.

Comparative Examples 1-4:

[0074]

Composition:	
73.2 mg, 64.5 mg, 54.8 mg, 37.7 mg	Soy bean phosphatidylcholine (SPC)
26.8 mg, 35.5 mg, 45.2 mg, 62.3 mg	Polysorbate (Tween 80)
1 mg/g	Triamcinolone acetonide
899 mg	Phosphate buffer (10mM, pH 6.5)

Preparation:

[0075] Various SPC and triamcinolone acetonide amounts (as specified) are dissolved in 50 mL chloroform and 50 mL methanol. The solvent, which is kept warm (approx. 40 degrees Celsius), is evaporated under a stream of nitrogen and the residue is dried in vacuum at room temperature. Tween 80 in the specified quantity and phosphate buffer is added to the lipid film and the resulting crude suspension is sonicated to prepare smaller mixed lipid vesicles. The resulting suspension should be opalescent and slightly yellow, which requires up to a few minutes of sonication, and is stable for at least I day. The test sample is used within 24 h after the preparation.

Biological and/or characterisation experiments:

[0076] The following suspensions were done as described further below.

Examples 4-5:

[0077]

Composition:	
37.74 mg	Soy bean phosphatidylcholine (SPC)
62.26 mg	Tween 80
0.4 mg	Triamcinolone Acetonide
0, 26.25 mg	Benzyl alcohol
4.47 g	Phosphate buffer 50 mM pH 6.5
0.3 mg	Probucol
0.3 mg	Desferal

Preparation:

[0078] SPC, probucol and triamcinolone acetonide are dissolved in a chloroform/methanol mixture. Dry lipid mixture is prepared as described for example 1. Desferal, Tween 80, and 894.23 mg buffer is added to the dry lipid. The resulting suspension is stirred over night. After adding, if so chosen, 26.25 mg benzyl alcohol in 3.58 g buffer to the suspension, the mixture is extruded through a 200 nm polycarbonate membrane and then through a 50 nm membrane using sufficient excess pressure to give an acceptable flow rate. The resulting particle diameter is below 150 nm

Example 6:

[0079]

Composition:	
37.74 mg	SPC
62.26 mg	Tween 80
35 mg	Ethanol
0.4 mg	Triamcinolone acetonide
26.25 mg	Benzyl alcohol

(continued)

Composition:	
4.47 g	Phosphate buffer (50 mM pH 6.5)
0.3 mg	Probucol
0.3 mg	Desferal

Preparation:

[0080] SPC, probucol and triamcinolone Acetonide are dissolved in ethanol. Desferal, Tween 80,5.25 mg benzyl alcohol and 894.23 mg buffer is added. The resulting suspension is stirred over night. The following day a solution of 21 mg benzyl alcohol in 3.58 g buffer is added to the suspension. The suspension is extruded , first, through a 200 nm pore polycarbonate membrane and then through a 50 nm membrane. This results in particle radius around 60 nm.

[0081] Analysis of formulation stability by means of HPLS suggests that the presence of probucol and desferal is advantageous to the chemical stability of suspension.

Comparative Examples 7-14:

[0082]

Composition:	
88.1 g, 87.4 g, 86.6 g, 85.75 g	Soy bean phosphatidylcholine (SPC)
11.9 g, 12.6 g, 13.4 g, 14.25 g	Sodium cholate (NaChol)
80 g	Ethanol
0.5 g	Triamcinolone acetonide
ad 1000 g	Phosphate buffer (pH 7.1)

Preparation:

[0083] SPC and triamcinolone acetonide are dissolved in ethanol, to which NaChol is also added (which dissolves only partially). After the addition of buffer, the resulting turbid, whitish suspension is stirred over night. To bring the vesicles to final size, the suspension is either: extruded through a 200 nm membrane and then through a 100 nm membrane under pressure; 2) processed by a high pressure homogeniser (run in the low pressure range, e.g. at 200 psi) to yield an opalescent final suspension.

[0084] From the preparation made as described above, two alternative formulations were made by diluting the suspension with a buffer (containing 0.5 V-% benzyl alcohol) to a final total lipid concentration of 5 w-% and 2 w-%, respectively.

Comparative Examples 15-49:

[0085]

Composition:	
377.4 mg	Soy bean phosphatidylcholine (SPC)
622.6 mg	Tween 80
50 mg	Benzyl alcohol
9000 mg	Phosphate buffer 50 mM pH 6.5
a) 12.5 mg, 25 mg, 50 mg,	Bethamethasone
b) 12.5 mg,25 mg, 50 mg,	Bethamethasone dipropionate
c) 12.5 mg,25 mg, 50 mg	Bethamethasone 17 valerate
d) 12.5 mg,25 mg, 50 mg	Clobetasol-17-propionate
e) 12.5 mg,25 mg, 50 mg	Dexamethasone or
f) 25 mg, 50 mg, 75 mg,	Hydrocortisone

(continued)

Composition:	
g) 12.5 mg,25 mg, 50 mg	Prednicarbate
h) 0.75 mg, 12.5 mg, 25 mg	Triamcinolone

Preparation:

[0086] SPC and the corticosteroid of choice is dissolved in ethanol. After the addition of buffer, which also contains Tween 80 and benzyl alcohol, the resulting highly turbid suspension is thoroughly mixed for at least 24 h, and more preferably for several days. The suspension is then extruded through a 200 nm membrane, if required several times. The resulting suspension of vesicles, which are still relatively large, tends to sediment with time, however, but can be re-homogenised easily by swirling or another gentle mixing method. To get vesicles with smaller final size, and thus a more stable suspension, a final extrusion through a 100 nm membrane is useful. (Vesicles with the highest given drug concentration may contain some drug in the suspension, perhaps in the form of vesicle coated drug crystals.)

Comparative Example 50:

[0087]

Composition:	
347 mg	Soy bean phosphatidylcholine (SPC)
623 mg	Tween 80
30 mg	Sodium dodecyl sulphate (SDS)
50 mg	Benzyl alcohol
9000 mg	Phosphate buffer 50 mM pH 6.5
25 mg	Clobetasol-17-propionate

Preparation:

[0088] Corticosteroid suspension was prepared as described in previous examples, except in that SDS was added dissolved in buffer to act as drug distribution promotor in the target organ.

[0089] Formulation containing SDS acts significantly more rapidly in human skin blanching assay than the SDS-free formulation.

[0090] Hereinfurther are described some preclinical experiences with the hydro-lotion-like formulations based on highly adaptable agent carriers, i.e. highly adaptable and flexible lipid vesicles (Transfersomes™; cf. above-cited references) of several corticosteroids in vitro and in vivo. These novel, carrier-based formulations are shown to give rise to the desired drug concentrations in the skin after a single application of the agent in Transfersomes. Depending on amount of carrier used, a localized (intracutaneous) or a local and systemic (whole body) delivery is possible.

[0091] The new corticosteroid delivery concept promises to lower the danger of adverse side effects of the topical therapy with such medication. This is possible due to dose-lowering and a different drug delivery mechanism: Corticosteroids in Transfersomes can not penetrate directly into the blood vessels, owing to the prohibitively large size of the carriers. Such drugs are thus confined to the intercellular space, where they can exert their desired biological function. (Only when they are applied in ample amounts such therapeutics are distributed throughout the body, first via the lymphatic and then through blood circulation.)

[0092] Data measured in animals and humans suggest that several widely used corticosteroids can be nearly prevented from reaching the blood if they are placed on the skin in a suspension of Transfersomes. One can argue that this phenomenon relies on the extremely high deformability of transfersome membranes, which permits the drug carriers to pass the skin
permeability barrier. The good control over this penetration process and the exclusion of intravasation enables the restriction of the biological effects of transfersomal corticosteroids nearly exclusively to the treated skin. The different vaso-constriction induced by corticosteroids in creams/lotions or Transfersomes indirectly support this conclusion. The use of highly deformable carriers increases the potency of corticosteroids up to one order of magnitude in relation to previous, commercial formulations. This fact also improves the final drug safety. (The area-dose needed for the Transfersomes-mediated therapeutic success of dexamethasone or triamcinolone acetonide in the treated skin surface must reach 1.5 m^2 before the total applied drug amount matches that of native hydrocortisone in the blood.)

In vitro Penetration Studies

[0093] The differential penetration capability of various drug and drug-carrier formulations through an artificial transport barrier clearly demonstrates the relative advantage of ultradeformable Transfersomes in comparison with, for example, standard liposomes.While the latter are nearly completely incapable of crossing such an artificial skin barrier', Transfersomes pass through the fine openings in such a barrier essentially unhindered. The following table illustrates this behavior.

Table 1:

Capability (relative to water) of the corticosteroid-loaded Transfersomes, liposomes and micelles to penetrate through the pores 3-4 times smaller than the penetrant size under the influence of hydrostatic pressure. [a)]		
Formulation	**Low pressure (0.2 MPa)**	**High pressure (0.9 MPa)**
Micelles	1.1 ± 0.1	1.1 ± 0.1
Liposomes	≤ 0.0001	≤ 0.001
Transfersomes	≤ 0.001	1 ± 0.1
Liposomes with hydrocortisone	≤ 0.0001	≤ 0.001
Transfersomes with hydrocortisone	≤ 0.001	1 ± 0.1
Transfersomes with dexamethasone	≤ 0.001	1 ± 0.1
Transfersomes with triamcinolone-acetonide	≤ 0.001	1 ± 0.1

a) The artificial barrier consisted of a polycarbonate membrane perforated by the pores of 100 nm diameter. Liposomes and Transfersomes had comparable size. The quoted transport efficacy corresponds to the ratio of aggregate-to-water transport rate measured under identical conditions (by HPLC and gravimetry, respectively).

[0094] When applied onto the intact skin surface, phospholipid suspensions are not detrimental to the skin. On the contrary: certain phospholipid preparations have been reported to improve the hydration (and thus to a minor extent the optical appearance) of the aging skin. Phospholipid suspensions are also non-irritating to the skin, at least up to the degree of 30% degradation.

Corticosteroid preparations on the basis of transfersomes will normally be used in a quantity (around 100 mg per 2 days) that will contain lipid amounts comparable to those used parenterally (≤ 75 mg/injection) or orally (≤ 150 mg/day). The recommended daily dose of transfersomal corticosteroids for human use will be appreciably lower (≤ 25 mg), except in the case of hydrocortisone, where a somewhat higher dosage might be required for a whole body therapy. Total phospholipid amount to be placed on the skin in the form of transfersomes-based corticosteroid formulations will always be less than 0.5 g/day. It is also less than 10% of the natural variability of phosphatidylcholine concentration in the plasma of an average, healthy person. In light of these data given below, one can conclude that the corticosteroidal dermatics based on transfersomes from the carrier point of view will be an extremely safe product.

[0095] From the agent point of view, a maximum corticosteroid amount (1 mg/day for dexamethasone or triamcinolone-acetonide and below 20 mg for hydrocortisone) comparable to that produced in the body (12 mg to 30 mg of hydrocortisone per day) will be applied topically. The area dose will normally be between 0.1 μg cm^{-2} and 1 μg cm^{-2}, for the high and low potency drugs, respectively. Only a tiny fraction of the epicutaneously drug is likely to appear in the circulation, however, as can be seen from the following table.

Table 2:

The ratio of corticosteroid concentration in the blood and in the 'inner skin' of mice (measured) and humans (calculated).						
Dose ($\mu g/cm^{-2}$)	Hydrocortisone (mouse)	Hydrocortisone (human)	Dexamethasone (mouse)	Dexamethasone (human)	Triamcinolone-acetonide (mouse)	Triamcinolone-acetonide (human)
0.5	0	0	0	0		
1.3					0.02	0.00007
4.9	0.012	0.000004	0.1	0.00003		
13.2					0.04	0.00011
20.6					0.03	0.0001
49.5	0.015	0.000005	0.25	0.00009		

[0096] It can, therefore, be anticipated that corticosteroids based on transfersomes will cause less side effects, if any, than the currently available commercial formulations of such drugs. This, on the one hand, is due to the more favorable bio-distribution of the drugs from the transfersomes, which is concentrated to the tissue to be treated. On the other hand, drugs from the carriers are likely to be taken in relatively higher proportions by the strongly proliferating cells, which are one of the chief natural targets for the corticosteroid therapy. (It is even possible that very low doses of transfersomal corticosteroids will completely eliminate the problem of skin atrophy after the repeated use of such therapeutics.)

[0097] Even more relevant, for the assessment of practical values of transfersomal corticosteroids, are the results obtained in validated animal trials, which are described in the following section.

Preclinical Studies

[0098] All substances used in this study were of pharmaceutic quality. Soybean phosphatidylcholine (SPC) was purchased from Lipoid KG (Ludwigshafen, Germany) or Nattermann Phospholipids - Rhone-Poulenc Rorer (Köln, Germany) and was more than 95 % pure. The remaining components, which are described in detail in the above cited European patent, were from Henkel (Düsseldorf, Germany) or CPC (Hamburg, Germany). The active ingredients (dexamethasone, hydrocortisone, triamcinolone-acetonide) were purchased from Synopharm (Hamburg, Germany). The microbicides, chellators and antioxidants were from Ciba-Geigy (Basel, Switzerland) or Synopharm.

[0099] The bidistilled water in injectable quality was purchased from the local pharmacy. The commercial drug formulations from the local pharmacy were used for comparison (hydrocortisone: Hydrocortisone-Wolff (Wolff, Bielefeld); dexamethasone: Anemul (Pharmasal, Gräfelfing); triamcinolon-acetonide: Volon A Lotio N (Squibb-Hayden, München) and Delphicort-cream (Lederle, Wolfratshausen)).

[0100] **Drug in the Carrier (Transfersome) Suspensions.** The formulations used in the biodistribution studies were labelled with the tritiurated corticosteroids purchased from Amersham or ICN. Preparation of the formulations for the use in animals was done by dissolving all lipoids in methanol/chloroform (1/1 v/v) in the appropriate amounts and preparing a dry mixed lipid film under vacuum ($\leq$ 10 Pa; $\geq$ 12 h). The use of potentially harmful organic solvents or drying was entirely avoided in the manufacturing of human medications.

[0101] Formulations contained between 0.01 w-% and 0.5 w-% specified corticosteroid per mL of carrier suspension. The latter consisted chiefly of phosphatidylcholine (SPC) in a final concentration between 0.5 w-% and 5 w-%. This lipid was taken up in a buffer and homogenized (for animal experiments: by sonication with a titanium micro-tip, Heat Systems W 380, USA, 30 min, 4 °C; for human therapeutics by other mechanical means). At least one of the carrier components was characterized by its membrane solubilizing capacity, as is required by the basic rationale of Transfersome design and above-cited patent applications of the applicant. Such a embrane-affecting substance was always incorporated into the carriers in the sub-lytic concentration. This ensured the high carrier deformability without compromising the integrity of transfersome vesicles, since both is necessary for the high efficacy of drug carrier transport across the stratum comeum. The final vesicle size was determined with the photon correlation spectroscopy (90°, ALV-5000 ALV-Laser Vertriebsgesellschaft, Langen, Germany) and was typically between 100 nm and 200 nm. For experimental use, lipid suspension was diluted when appropriate. More detailed description and characterization data will be given separately.

[0102] **In vivo Experiments** mainly involved 8-12 weeks old NMRI mice which were kept under standard laboratory conditions (3-5 per suspending cage; standard chew and water ad libitum; 12 h light/dark regime). Stressful or painful manipulations were always carried out under general injection anesthesia.

[0103] **Biodistribution.** The hair at the chosen skin site was trimmed with a pair of scissors to the length of $\leq$ 2 mm one day before experimentation. The precise application site on the upper back was marked and the appropriate amount (0.5 µL to 25 µL) and drug formulation was applied with a micro-pipette on the skin. After uniform distribution with the side of the same pipette tip, the application was left to dry.

[0104] Blood samples (20 µL) were taken from the tail end with a glass capillary. After 8 hours the animals were killed by heart puncture and the treated skin area was undermined and carefully excised. The outermost layers of the stratum corneum were collected by five tape-strippings. Subsequently, the residual skin tissue and other organ samples were prepared, destained and used for radioactivity counting.

For the experiments with porcine skin, 20 x 30 cm^2 of full thickness organ was excised and fixed on a wet tissue. Several test areas of 1 cm^2 were then marked and treated further as in vivo.

[0105] Biological Action in mice was most often tested by measuring the suppression of a chemically induced edema by the topically administered corticosteroids. For this purpose, the test animals were first anesthetized with an intraperitoneal injection of 10 µL g^{-1} body weight of a mixture containing 6 mL 0.9 % NaCl, 1 mL Ketavet 100 (Parke-Davis, Berlin, FRG), and 0.25 mL Rompun (Bayer, Leverkusen, Germany). The appropriate amount of drug formulation was smeared over the inner side of one ear and left to dry out. When so stated, the ear was wiped free of the superficial formulation with a cotton swab. At a given time the test mouse was anesthetized and arachidonic acid in ethanol (1/2

V/V, 10 \muL) was applied to the same ear area. Change in the mouse ear edema (relatively to that of the untreated but challenged ear) was determined, either by measuring the ear thickness with a micro-caliper (our method) or by weighing the ear volume of the killed mouse (original procedure). Both these assays deliver similar results. All values are the means of at least 3 independently measured values and bars give standard deviation of their mean.

Human Studies

[0106] According to the scientific literature, it is customary to test the biological potency of different corticosteroid preparations in humans by a so-called 'skin blanching' assay. Such a test is not as adequate for the investigation of carrier-based corticosteroids, as it is for the testing of the corresponding drug solutions for the reasons given below. This notwithstanding, the topical vase-constriction test was used to compare the kinetics of corticosteroid action on the rodent and human skin.

[0107] In a pilot trial with three human volunteers, the test formulations were applied to one arm at different doses in parallel rows. By using a high precision micropipette, individual areas of 1 cm^2 were covered. The vaso-constriction over each such skin domain was then determined by visual inspection (at least once by an independent observer who was unaware of the drug application pattern) and the skin blanching score was identified with the number of well defined square corners or edges.

[0108] Human skin was shown to respond similarly to the topical administration of corticosteroids in Transfersomes when compared to murine skin: after approximately 7 h the vaso-constriction (skin blanching) effect reaches 50 % of its maximum value and saturates at $t \geq 8$ h. A high biological activity is observed for at least 32 h, with final decay to 50 % level observed between 36 h and 48 h, provided the administered drug dose is around 1 $\mu g\ cm^{-2}$ (Figure 4).

[0109] Similar evolution of skin blanching is observed after the topical administration of triamcinolone-acetonide in a commercial cream, but not before the drug dose has exceeded 10 $\mu g\ cm^{-2}$. Skin palor in the early phase ($8 \leq t/h \leq 16$) after cream application is deeper (whiter) and appears faster than in the case of the cortico-Transfersomes-mediated vaso-constriction. In our opinion, this is due to the restricted ability of transfersome-associated drugs to get into the blood capillaries. This phenomenon is not encountered with the drugs in commercial formulations, which allow diffusiong through and beyond the skin in monomeric (or at least dissociated) form. This explains the faster onset of (the desired) edema-suppression action and the retardation of (the rather undesired) vaso-constriction, which is an indication of drug spill-over into the blood circulation. (The relatively sluggish appearence of Transfersomes-mediate edema-suppression is also due to the poor responsiveness of one test person, who reacted to the drug in Transfersomes slowly and did not react to the low dose of commercial creme at all, the latter lack of effect not being seen in the time-course of average drug action.)

Results

[0110] from the representative experiments are shown in the attached figures.

[0111] Upper panel of Figure 1 illustrates the biological edema-suppression activity of hydrocortisone in commercial cream (open symbols) and in the highly adaptable lipid vesicles, Transfersomes, (closed symbols). Data give mean values measured from 3-4 animals and error bars represent the corresponding standard deviations.

[0112] Lower panel of Figure 1 shows dose versus action, as assessed in the local edema-suppression tests, of hydrocortisone in a commercial cream (open symbols) and transfersomal suspension (closed symbols) after 16 h of action. (The maximum in dose vs. action curve is due to the dose dependence of action kinetics (see also figure 2).)

[0113] From Figure 1 can be seen that the biological effect of hydrocortisone in Transfersomes™-based formulation significantly exceeds that of the more conventional cream-like formulation containing similar drug - the lower is the administered drug-dose per area the higher is the resulting therapeutic advantage. These data suggest that it should be possible to make, and sell with an excellent commercial perspective, the (hydro)lotion-like hydrocortisone formulation containing just 0.1 % of the drug. This unprecedented low agent content may reduce the danger of side effects.

[0114] Upper panel of Figure 2 illustrates suppression of the arachidonic acid-induced edema by dexamethasone in the commercial cream (open symbols) or Transfersomes (closed symbols) as the function of time after drug administration on the intact murine skin. In both cases the excess drug was wiped-away from the application site 8 h after administration.

[0115] Lower panel shows effect of changing the dose per area on the dexamethasone-mediated suppression of skin edema in the murine ear model. (Different symbols give results from the different experimental series; for further details see figure 1.)

[0116] As a result from Figure 2 it is obvious that owing to its higher intrinsic potency, dexamethasone exerts a much stronger biological effect than hydrocortisone when tested locally on the challenged skin. The incorporation of dexamethasone into the ultradeformable agent carriers, Transfersomes further improves this therapeutic advantage. The benefit of using Transfersomes is most dramatic when the excess drug is eliminated from the treated skin site (as in

real life). It is expected that drug formulations with merely 0.02 % dexamethasone ('strong') or with just around 0.005 % dexamethasone ('gentle') in Transfersomes will be needed for an adequate skin treatment.

[0117] Upper panel of Figure 3 illustrates the biological anti-edema activity of triamcinolone-acetonide in commercial lotion (open symbols) or in Transfersomes (closed symbols) in the murine ear model whereas lower panel shows dose vs. action curve for triamcinolone-acetonide in Transfersomes (full symbols, two different preparations and test series), commercial cream (open boxes) or commercial lotion (open circles) applied on the intact murine skin.

[0118] The biological potency of triamcinolone-acetonide in commercial products is thus 10-times lower than that of the drug in a suspension of Transfersomes. The latter also prolong the duration of therapeutic effect by the same order of magnitude. In comparison with transfersomal dexamethasone, triamcinolone-acetonide in the ultradeformable agent carriers exerts a somewhat stronger but moderately less persistent biological function. The anticipated drug concentration for the commercial formulation on the basis of Transfersomes is between 0.005 % and 0.02 %.

[0119] Figure 4 shows vaso-constriction (blanching-assay) in the intact human skin as a function of time, following an epicutaneous administration of triamcinolone-acetonide in Transfersomes (upper panel) or in commercial cream (lower panel).

[0120] It thus can be seen that the 'therapeutic effect' on the human skin of the high potency corticosteroid applied in Transfersomes is dramatically better than that of the conventional triamcinolone-acetonide cream. A single topical drug administration with Transfersomes ensures good biological function for more than a day, with a dose of 1 $\mu g\ cm^{-2}$. While the commercial cream causes a rather short-term 'deep blanching', the Transfersomes-based formulations mediates a more gradual and long-lasting superficial vaso-constriction. This is indicative of reduced drug spill-over into the circulation from the carrier-based formulation (see also the figures on the following two pages).

[0121] In Figure 5 differerent drug penetration profiles in the mammalian skin are shown. The data were measured in vivo in mice (left panel) and ex vivo in porcine skin (right panel). Open symbols represent measurements with a commercial cream and closed symbols with the suspension of dexamethasone-loaded Transfersomes.

[0122] The use of Transfersomes for carrying corticosteroids in the skin flattens the drug penetration profile in the skin. The relative drug concentration increases in the deeper skin region, when compared to the results achieved with the commercial formulation of similar drug.

[0123] Figure 6 illustrates corticosteroid accumulation (retention) in the skin after administration by means of Transfersomes on the intact surface. (∇ and Δ correspond to the inner and outer skin regions and $\Diamond$ gives their sum.)

[0124] As a result transfersomes bring a relatively high proportion of the epicutaneously administered drug into the viable skin.

[0125] Figure 7 illustrates using of Transfersomes for the transcutaneous corticosteroid delivery into the systemic circulation.

[0126] Choosing suitably optimized agent carriers (good Transfersomes) as well as proper dose per area allows for systemic delivery. Lowering the dose per area increases the relative drug concentration at the site of epicutaneous carrier administration.

[0127] In Figure 8 relative efficiency of various triamcinolone acetonide formulations as tested by the murine ear edema assay is shown. Comparison of the biological activity of two different kinds of Transfersomes loaded with this drug (upper panel), a commercial cream (lower panel) and of conventional liposomes (lower panel). The latter two data sets are not statistically significant even at the level of 0.1.

[0128] In order to maximize the efficacy of intracutaneous drug delivery and to achieve good biological effects it is necessary to employ the specially optimized, proprietary agent carriers, Transfersomes. The replacement of such highly deformable Transfersomes by simple, conventional liposomes produces results that are not better than those obtained by the commercial creams (or lotions).

Claims

1. Formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, provided that the penetrants can transport agents or else enable agent permeation through the pores after penetrants have entered pores, the agents associated with said penetrants being corticosteroids, especially glucocorticoids or mineralocorticosteroids, **characterized in that** the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation, and
   the formulation comprises at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100 % per 6 months.

2. Formulation according to claim 1,
   characterised in that the formulation comprises at least one consistency builder in an amount that increases the

formulation viscosity above that of the non-thickened corresponding formulation to maximally 5 Ns/m^2 so that spreading over, and retention at, the application area is enabled and/or at least one microbicide in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days.

3. Formulation according to claim 2,
characterized in that said at least one consistency builder is added in an amount that increases the formulation viscosity to up to 1 Ns/m^2 and more preferably to up to 0.2 Ns/m^2.

4. Formulation according to claims 1 to 3,
characterised in that said at least one antioxidant is added in an amount that reduces the increase of oxidation index to less than 100 % per 12 months and more preferably to less than 50 % per 12 months.

5. Formulation according to claims 2 to 4,
characterised in that said at least one microbicide is added in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 3 days, and more preferably after a period of 1 day.

6. Formulation according to any of claims 2 to 5,
characterised in that the consistency builder is selected from pharmaceutically acceptable hydrophilic polymers, such as partially etherified cellulose derivatives, comprising carboxymethyl -, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl- or methyl-cellulose; completely synthetic hydrophilic polymers comprising polyacrylates , polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate, polyacrylonitrile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols, poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, (hydrazine cross-linked) hyaluronic acid, silicone; natural gums comprising alginates, carrageenan, guar-gum, gelatine, tragacanth, (amidated) pectin, xanthan, chitosan collagen, agarose; mixtures and further derivatives or co-polymers thereof and/or other pharmaceutically, or at least biologically, acceptable polymers.

7. Formulation according to claim 6,
characterised in that the polymer weight fractions are in the range between 0.05 % and 10%, more preferably are in the range between 0.1% and 5 %, even more preferably are in the range between 0.25 % and 3.5 % and most preferably are in the range between 0.5 % and 2 %.

8. Formulation according to any one of claims 1 to 7,
characterised in that the anti-oxidant is selected from synthetic phenolic antioxidants, such as butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethyl-hydroquinone (HTHQ); aromatic amines, including diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol and tetrahydroindenoindol; phenols and phenolic acids, including guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA) and eugenol; tocopherols and their derivatives, including tocopheryl-acylate, -laurate, myristate, -palmitate, -oleate,-linoleate, or any other suitable tocopheryl-lipoate, tocopheryl-POE-succinate; trolox and corresponding amide and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters, including 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid; non-steroidal anti-inflammatory agents (NSAIDs), such as indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminephen; aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics, including amiodarone, aprindine and asocainol; ambroxol, tamoxifene, b-hydroxytamoxifene; calcium antagonists, including nifedipine, nisoldipine, nimodipine, nicardipine and nilvadipine, beta-receptor blockers including atenolol, propranolol and nebivolol; sodium bisulphite, sodium metabisulphite, thiourea; chellating agents, such as EDTA, GDTA, desferral; miscellaneous endogenous defence systems, such as transferrin, lactoferrin, ferritin, cearuloplasmin, haptoglobion, haemopexin, albumin, glucose, ubiquinol-10; enzymatic antioxidants, such as superoxide dismutase and metal complexes with a similar activity, including catalase, glu-

tathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids including flavones, flavonols, flavonones, flavanonals and chacones, anthocyanins; N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamatic acids and their esters, including coumaric acids and esters caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid and sinapic acid; spice extracts, including spice extracts from clove, cinnamon, sage, rosemary, mace, oregano, allspice and nutmeg; carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives, including U74006F; tryptophan metabolites, including 3-hydroxykynurenine and 3-hydroxyanthranilic acid; and organochalcogenides.

9. Formulation according to claim 8,
characterised in that the concentration of BHA or BHT is between 0.001 and 2 w-%, more preferably is between 0.0025 and 0.2 w-%, and most preferably is between 0.005 and 0.02 w-%, of TBHQ and PG is between 0.001 and 2 w-%, more preferably is between 0.005 and 0.2 w-%, and most preferably is between 0.01 and 0.02 w-%, of tocopherols is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.075 w-%, of ascorbic acid esters is between 0.001 and 5, more preferably is between 0.005 and 0.5, and most preferably is between 0.01 and 0.15 w-%, of ascorbic acid is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.1 w-%, of sodium bisulphite or sodium metabisulphite is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01-0.15 w-%, of thiourea is between 0.0001 and 2 w-%, more preferably is between 0.0005 and 0.2, and most preferably is between 0.001-0.01 w-%, most typically 0.005 w-%, of cysteine is between 0.01 and 5, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1 and 1.0 w-%, most typically 0.5 w-%, of monothioglycerol is between 0.01 and 5 w-%, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1-1.0 w-%, most typically 0.5 w-%, of NDGA is between 0.0005-2 w-%, more preferably is between 0.001-0.2 w-%, and most preferably is between 0.005-0.02 w-%, most typically 0.01 w-%, of glutathione is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.2 w-%, most typically 0.1 w-%, of EDTA is between 0.001 and 5 w-%, even more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.2 w-%, most typically between 0.05 and 0.975 w-%, of citric acid is between 0.001 and 5 w-%, even more preferably is between 0.005 and 3 w-%, and most preferably is between 0.01-0.2, most typically between 0.3 and 2 wt-%.

10. Formulation according to any one of claims 2 to 9,
characterised in that the microbicide is selected from short chain alcohols, comprising ethyl and isopropyl alcohol, chlorbutanol, benzyl alcohol, chlorbenzyl alcohol, dichlorbenzylalcohol, hexachlorophene; phenolic compounds, such as cresol, 4-chloro-m-cresol, p-chloro-m-xylenol, dichlorophene, hexachlorophene, povidon-iodine; parabenes, especially alkyl-parabenes, such as methyl-, ethyl-, propyl-, or butyl- paraben, benzyl paraben; acids, such as sorbic acid, benzoic acid and their salts; quaternary ammonium compounds, such as alkonium salts, e. g. a bromide, benzalkonium salts, such as a chloride or a bromide, cetrimonium salts, e.g. a bromide, phenoalkecinium salts, such as phenododecinium bromide, cetylpyridinium chloride and other salts; mercurial compounds, such as phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, or any antibiotically active compounds of biological origin, or any mixture thereof.

11. Formulation according to claim 10,
characterised in that the bulk concentration of short chain alcohols in the case of ethyl, propyl, butyl or benzyl alcohol is up to 10 w%, more preferably is up to 5 w-%, and most preferably is in the range between 0.5-3 w-%, in the case of chlorobutanol is in the range between 0.3-0.6 w-%; bulk concentration of parabens, especially in the case of methyl paraben is in the range between 0.05-0.2 w-%, and in the case of propyl paraben is in the range between 0.002 - 0.02 w-%; bulk concentration of sorbic acid is in the range between 0 .05-0.2 w-%, and in the case of benzoic acid is in the range between 0.1-0.5w- %; bulk concentration of phenols, triclosan, is in the range between 0.1-0.3 w-%, and bulk concentration of chlorhexidine is in the range between 0.01-0.05 w-%.

12. Formulation according to any one of the preceding claims,
characterised in that the corticosteroid is selected from alclonetasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone, betamethasone 17-valerate, betamethasone 17,21-divalerate, betamethasone 21-acetate, betamethasone 21-buytrate, betamethasone 21-propionate, betamethasone 21-valerate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, cortexolone, corticosterone, cortisone, cortisone 17-acetate, 21-deoxybetamethasone, 21-deoxybetamethasone 17-propionate, deoxycorticosterone, desonide, desoxymethasone, dexamethasone, di-

florasone diacetate, diflucortolone valerate, fluclorolone acetonide, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, 9-alpha-fluorocortisone, 9-alpha-fluorohydrocortisone, 9-alpha-fluoroprednisolone, fluprednidene acetate, flurandrenolone, halcinonide, hydrocortisone, hydrocortisone 17-acetate, hydrocortisone 17-butyrate, hydrocortisone 17-propionate, hydro cortisone 17-valerate, hydrocortisone 21-acetate, hydrocortisone 21-butyrate, hydrocortisone 21-propionate, hydrocortisone 21-valerate, 17-alpha-hydroxyprogesterone, methylprednisolone acetate, mometasone furoate, prednisolone, prednisone, prednisone 17-acetate, prednisone 17-valerate, progesterone, triamcinolone, triamcinolone acetonide.

13. Formulation according to any one of the preceding claims,
characterised in that the penetrants are suspended or dispersed in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, provided that said at least two substances differ by at least a factor of 10 in solubility in said liquid or else that said substances when in the form of homo-aggregates, for the more soluble substance, or of hetero-aggregates, for any combination of both said substances, have a preferred average diameter smaller than the diameter of the homo-aggregates containing merely the less soluble substance; or else provided that the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating in the vicinity of thermal energy.

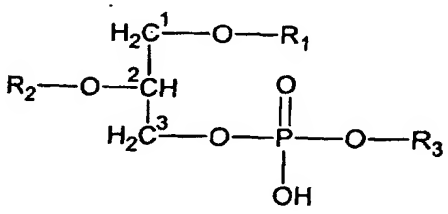
14. Formulation according to claim 13,
characterised in that the more soluble substance tends to solubilise the droplet and the content of such substance is up to 99 mol-% of solubilising concentration or else corresponds to up to 99 mol-% of the saturating concentration in the unsolubilised droplet, whichever is higher.

15. Formulation according to claim 14,
characterised in that the content of the more soluble substance is below 50 %, especially below 40 % and most preferably below 30 %, of said solubilising concentration of said substance.

16. Formulation according to claim 14,
characterised in that the content of the more soluble substance is below 80 %, preferably below 65 % and most preferably below 50 % of said saturation concentration of said substance in the droplet.

17. Formulation according to any one of claims 13 to 16,
characterised in that the less soluble amongst the aggregating substances is a lipid or lipid-like material, especially a polar lipid, whereas the substance which is more soluble in the suspending liquid and which increases the droplet adaptability belongs to surfactants or else has surfactant-like properties.

18. Formulation according to claim 17,
characterised in that the lipid or lipid-like material is a lipid or a lipoid from a biological source or a corresponding synthetic lipid or any of its modifications, said lipid preferably belonging to the class of pure phospholipids with the chemical formula



where R_1 and R_2 is an aliphatic chain, typically a C_{10-20}-acyl, or -alkyl or partly unsaturated fatty acid residue, in particular, an oleoyl-, palmitoeloyl-, elaidoyl-, linoleyl-, linolenyl-, linolenoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or stearoyl chain; and where R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_{1-4}-alkyl, C_{1-5}-alkyl substituted with carboxy, C_{2-5}-alkyl substituted with hydroxy, C_{2-5}-alkyl substituted with. carboxy and hydroxy, or C_{2-5}-alkyl substituted with carboxy and amino, inositol, sphingosine, or salts of said substances, said lipid comprising also glycerides, isoprenoid lipids, steroids, sterines or sterols, of sulphur- or carbohydrate-containing lipids, or any other bilayer-forming lipids, in particular half-protonated fluid fatty acids, said lipid is selected from the group comprising phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phos-

phatidylinositols, phosphatidic acids, phosphatidylserines, sphingomyelins or other sphingophospholipids, glycosphingolipids (including cerebrosides, ceramidepolyhexosides, sulphatides, sphingoplasmalogens), gangliosides and other glycolipids or synthetic lipids, in particular with corresponding sphingosine derivatives, or any other glycolipids, whereby two similar or different chains can be ester-groups-linked to the backbone (as in diacyl and dialkenoyl compound) or be attached to the backbone with ether bonds, as in dialkyl-lipids.

19. Formulation according to claim 17,
characterised in that the surfactant or surfactant-like material is a nonionic, a zwitterionic, an anionic or a cationic surfactant, especially a fatty-acid or -alcohol, an alkyl-tri/di/methylammonium salt, an alkylsulphate salt, a monovalent salt of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, an acyl- or alkanoyl-dimethyl-aminoxide, esp. a dodecyl- dimethyl-aminoxide, an alkyl- or alkanoyl-N-methylglucamide, N-alkyl-N,N- dimethylglycine, 3-(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a polyethyleneglycol-octylphenyl ether, esp. a nonaethylene-glycol-octylphenyl ether, a polyethylene-acyl ether, esp. a nonaethylen-dodecyl ether, a polyethylene-glycol-isoacyl ether, esp. a octaethylene-glycol-isotridecyl ether, polyethyleneacyl ether, esp. octaethylenedodecyl ether, polyethylene-glycol-sorbitane-acyl ester, such as polyethylenglykol-20-monolaurate (Tween 20) or polyethylenglykol-20-sorbitan-monooleate (Tween 80), a polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene-lauryl, -myristoyl, -cetylstearyl, or -oleoyl ether, as in polyhydroxyethylene-4 or 6 or 8 or 10 or 12, etc., -lauryl ether (as in Brij series), or in the corresponding ester, e.g. of polyhydroxyethylen-8-stearate (Myrj 45), -laurate or -oleate type, or in polyethoxylated castor oil 40, a sorbitane-monoalkylate (e.g. in Arlacel or Span), esp. sorbitane-monolaurate, an acyl- or alkanoyl-N-methylglucamide, esp. in or decanoyl- or dodecanoyl-N-methylglucamide, an alkyl-sulphate (salt), e.g. in lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium glycodeoxycholate, sodium oleate, sodium taurate, a fatty acid salt, such as sodium elaidate, sodium linoleate, sodium laurate, a lysophospholipid, such as n-octadecylene(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-acyl-, e.g. lauryl or oleoyl-glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-tetradecyl- glycero-phosphatidic acid, -phosphorylglycerol, or -phosphorylserine, a corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospholipid or a corresponding short-chain phospholipid, or else a surface-active polypeptide.

20. Formulation according to any one of claims 13 to 19,
characterised in that the average penetrant diameter is between 30 nm and 500 nm, preferably between 40 nm and 250 nm, even more preferably between 50 nm and 200 nm and most preferably between 60 nm and 150 nm.

21. Formulation according to any one of claims 13 to 19,
characterised in that the average diameter of the penetrant is 2 to 25 times bigger than the average diameter of the pores in the barrier, preferably between 2.25 and 15 times bigger, even more preferably between 2.5 and 8 times bigger and most preferably between 3 and 6 times bigger than said average pore diameter.

22. Formulation according to any one of claims 13 through to 21,
characterised in that the dry weight of all carrier droplets in a formulation for the use on human or animal skin is 0.01 weight-% (w-%) to 40 w-% of total formulation mass, in particular between 0.1 w-% and 30 w-%, particularly preferably between 0.5 w-% and 20 w-%, and most preferably between 1 w-% and 10 w-%.

23. Formulation according to any one of claims 13 through to 21,
characterised in that the dry weight of all carrier droplets in a formulation for the use on human or animal mucosa is 0.0001 w-% to 30 w-% of total formulation mass.

24. Formulation according to any one of the claims 1 through to 23,
characterised in that the pH of carrier suspension is between 4 and 10, preferably between 5 and 9, and even more often up to 8.5, as required to maximise the stability of formulation.

25. A method for preparing a formulation for non-invasive application in vivo, according to any one of the preceding claims,
characterised in that penetrants capable of associating and/or incorporating said agent molecules are formed from at least one amphiphilic substance, at least one polar fluid, at least one edge-active substance or surfactant, at least one corticosteroid in an amount of more than 0.1 w-% based on total dry mass of the formulation, and, in case, other customary ingredients, which together form said formulation.

26. The method of claim 25,

characterised in that at least one edge-active substance or surfactant, at least one amphiphilic substance, at least one hydrophilic fluid and the agent are dissolved to form a solution and, if required, are mixed separately, the resulting (partial) mixtures or solutions then being combined to subsequently induce, preferably by action of mechanical energy, such as shaking, stirring, vibrating, homogenising, ultrasonication, shear, freezing and thawing, or filtration using convenient driving pressure, the formation of penetrants that associate with and/or incorporate the agent.

27. The method of claims 25 or 26,
characterised in that said amphiphilic substances are either used as such, or dissolved in a physiologically compatible polar fluid, which may be water or miscible with water, or in a solvation-mediating agent, together with a polar solution.

28. The method of claims 25 or 26,
characterised in that said amphiphilic substances are dissolved in highly volatile alcohols, in especially ethanol, or in pharmaceutically acceptable organic solvents, which are then removed, esp. by evaporation, prior to making final preparation.

29. The method as claimed in claims 27 or 28,
characterised in that the polar solution contains at least one edge-active substance or surfactant.

30. The method according to any one of claims 25 through to 29,
characterised in that the formation of said penetrants is induced by the addition of required substances into a fluid phase, evaporation from a reverse phase, by injection or dialysis, if necessary under the influence of mechanical stress, such as shaking, stirring, in especially high velocity stirring, vibrating, homogenising, ultrasonication, shearing, freezing and thawing, or filtration using convenient, in especially low (1 MPa) or intermediate (up to 10 MPa), driving pressure.

31. The method of claim 30,
characterised in that the formation of said penetrants is induced by filtration, the filtering material having pores sizes between 0.01 μm and 0.8 μm, preferably between 0.02 μm and 0.3 μm, and most preferably between 0.05 μm and 0.15 μm, whereby several filters may be used sequentially or in parallel.

32. The method according to any one of claims 25 through to 31,
characterised in that said agents and penetrants are made to associate, at least partly, after the formation of said penetrants, e.g. after injecting a solution of the drug in a pharmaceutically acceptable fluid, such as ethanol, 1-and 2-propanol, benzyl alcohol, propylene glycol, polyethylene glycol (molecular weight: 200 - 400 D) or glycerol into the suspending medium, said penetrants being formed previously, using the corresponding or some other suitable manufacturing method, or simultaneously with the drug injection, if required using a co-solution of the drug and, at least some, penetrant ingredients.

33. The method according to any one of the claims 25 through to 32,
characterised in that said penetrants, with which the agent molecules are associated and/or into which the agent is incorporated, are prepared just before the application of the formulation, if convenient from a suitable concentrate or a lyophylisate.

34. Formulation according to any one of claims 1 through to 24,
characterised in that the content of corticosteroids is between 0.1 w-% and 20 w-%, more preferably between 0.25 w-% and 10 w-% and even more preferably between 0.5 w-% and 5 w-%, relative to total dry mass of drug-loaded carriers.

35. Formulation according to claim 34,
characterised in that the relative content of corticosteroids in the case of triamcinolone or one of its derivatives, such as acetonide, is below 2 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 1 w-% and most preferably is below 0.5 w-%.

36. Formulation according to claim 34,
characterised in that the relative content of corticosteroids in the case of hydrocortisone or one of its derivatives is below 20 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 12.5 w-%

and most preferably is below 5 w-%.

37. Formulation according to claim 34,
characterised in that the relative content of corticosteroids in the case of dexamethasone or one of its derivatives is below 15 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 10 w-% and most preferably is below 5 w-%.

38. Formulation according to claim 34,
characterised in that the relative content of corticosteroids in the case of clobetasol or one of its derivatives, such as propionate is below 15 w-%, relative to total dry mass of the drug-loaded carriers, even more preferably is below 10 w-% and most preferably is below 5 w-%.

39. Formulation according to claims 34 to 38,
characterised in that the content of said corticosteroid is below the saturation maximum, defined as the content of corticosteroid at which the corticosteroid begins to crystallise in or outside the carrier.

40. Formulation according to claims 1 through to 24 and 34 through to 37,
characterised in that in order to speed up drug action a permeation enhancer is added.

41. Formulation according to claim 40,
characterised in that the permeation enhancer is selected from 1-acyl-azacycloheptan-2-ones (azones), 1-acyl-glucosides, 1-acyl-polyoxyethylenes, 1-acyl-saccharides, 2-n-acyl-cyclohexanones, 2-n-acyl-1,3-dioxolanes (SEPA), 1,2,3-triacyl-glycerols, 1-alkanols, 1-alkanoic acids, 1-alkyl-acetates, 1-alkyl-amines, 1-alkyl-n-alkyl-polyoxyethylenes, 1-alkyl-alkylates, n-alkyl-beta-D-thioglucosides, 1-alkyl-glycerides, 1-alkyl-propyleneglycols, 1-alkyl-polyoxyethylenes, (1-alkyl-)2-pyrrolidones, alkyl-acetoacetates, alkylene-glycols, alkylmethyl-sulphoxides (alkyl-DMSO), alkyl-propionates, alkyl-sulphates, diacyl-succinates, diacyl-N,N-dimethylaminoacetates (DDAA), diacyl-N,N-dimethylaminoisopropionates (DDAIP), phenyl-alkyl-amines.

42. Formulation according to claim 41,
characterised in that the bulk concentration range of the used enhancers is up to 5 % for 1-capryl-propylene glycol, 6-10 % for 1-[2-(decylthio)ethyl] azacyclopentan-2-one (=HPE-101), < 10% for 1-dodecanol, < 10 % for 1-dodecyl-azacycloheptan-2-one (=azone), about 10 % for 2-n-nonyl-1,3-dioxolane (SEPA), < 10 % for 2-n-octyl-cyclohexanone, up to 20 % for DMSO and between 5 % and 40 % for ethanol, at least 10 % for ethylene glycol, up to 30 % for ethyl acetate, 5-50 % for glycerol, up to 75 % for isopropanol, 1-20 % for isopropyl myristate, between 1 and 20 % for oleic acid and oleyl-alcohol, about 1 % for oleyl-polyoxyethylene-ether, at least 10 % forpropylene glycol.

43. Formulation according to claims 1 through to 24 and 34 through to 42,
characterised in that said corticosteroid is added in an amount which enables the formulation to be applied corresponding to an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between 0.1 mg cm^{-2} and 15 mg cm^{-2}, more preferably between 0.5 mg cm^{-2} and 10 mg cm^{-2}, particularly preferably between 0.75 mg cm^{-2} and 5 mg cm^{-2} and most preferably between 1 mg cm^{-2} and 2.5 mg cm^{-2}, if said corticosteroid is desired to exert a therapeutic effect in the deep subcutaneous, e.g. muscle or joints, tissue or else in the remote tissues, including the whole body.

44. Formulation according to claims 1 through to 24 and 34 through to 42,
characterised in that said corticosteroid is added in an amount which enables the formulation to be applied with an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between 1 μg cm^{-2} and 250 μg cm^{-2}, more preferably between 2.5 and 100 μg cm^{-2}, even more preferably between 5 μg cm^{-2} and 50 μg cm^{-2} and most preferably between 7.5 μg cm^{-2} and 20 μg cm^{-2}, if said corticosteroid is desired to exert a mainly local, that is, superficial, rather than systemic therapeutic effect.

45. Formulation according to claims I through to 24 and 34 through to 44,
characterised in that consistency and, if necessary other characteristics of the formulation are appropriately selected to enable spraying, smearing, rolling or sponging of the formulation on the application area in particular by using a sprayer, spender, roller or sponge, as appropriate.

46. Use of the formulations according to any one of the preceding claims for the preparation of a medicament for the

non-invasive application of corticosteroids, **characterised in that** the area dose, as expressed by the total dry mass of penetrant applied per unit area, is selected to be between 0.1 mg cm^{-2} and 15 mg cm^{-2}, preferably between 0.5 mg cm^{-2} and 10 mg cm^{-2}, particularly preferably between 0.75 mg cm^{-2} and 5 mg cm^{-2} and most preferably between 1 mg cm^{-2} and 2.5 mg cm^{-2}, if said corticosteroid is desired to exert a therapeutic effect in the deep subcutaneous, e.g. muscle or joints, tissue or else in the remote tissues, including the whole body.

47. Use of the formulations according to any one of the preceding claims for the preparation of a medicament for the non-invasive application of corticosteroids,
characterised in that the area-dose, as expressed by the total dry mass of penetrants applied per unit area, is between 1 µg cm^{-2} and 250 µg cm^{-2}, preferably between 2.5 µg cm^{-2} and 100 µg cm^{-2}, more preferably between 5 µg cm^{-2} and 50 µg cm^{-2} and most preferably between 7.5 µg cm^{-2} and 20 µg cm^{-2}, if said corticosteroid is desired to exert a mainly local, that is, superficial, rather than systemic therapeutic effect.

48. Use of the formulations according to any one of the preceding claims for the preparation of a medicament for the non-invasive application of corticosteroids associated with or encapsulated into said penetrants in the formulations, **characterised in that** the formulation is applied by spraying, smearing, rolling or sponging on the application area in particular by using a sprayer, spender, roller or sponge, as appropriate.

49. Use of a formulation in accordance with any one of the preceding claims for the preparation of a medicament for the treatment of inflammatory disease, dermatosis, kidney or liver failure, adrenal insufficiency, aspiration syndrome, Behcet syndrome, bites and stings, blood disorders, such as cold-haemagglutinin disease, haemolytic anemia, hypereosinophilia, hypoplastic anemia, macroglobulinaemia, trombocytopenic purpura, furthermore, for the management of bone disorders, cerebral oedema, Cogan's syndrome, congenital adrenal hyperplasia, connective tissue disorders, such as lichen, lupus erythematosus, polymyalgia rheumatica, polymyositis and dermatomyositis, epilepsy, eye disorders, such as cataracts, Graves'ophthalmopathy, haemangioma, herpes infections, neuropathies, retinal vasculitis, scleritis, for some gastro-intestinal disorders, such as inflammatory bowel disease, nausea and oesophageal damage, for hypercalcaemia, infections, e.g. of the eye (as in infections mononucleosis), for Kawasaki disease, myasthenia gravis, various pain syndromes, such as postherpetic neuralgia, for polyneuropathies, pancreatitis, in respiratory disorders, such as asthma, for the management of rheumatoid disease and osteoarthritis, rhinitis, sarcoidosis, skin diseases, such as alopecia, eczema, erythema multiforme, lichen, pemphigus and pemphigoid, psoriasis, pyoderma gangrenosum, urticaria, in case of thyroid and vascular disorders.

Patentansprüche

1. Formulierung umfassend Penetriermittel, die dazu in der Lage sind, die Poren einer Barriere zu durchdringen, auch wenn der durchschnittliche Durchmesser der genannten Poren kleiner ist als der durchschnittliche Durchmesser der genannten Penetriermittel, vorausgesetzt, dass die Penetriermittel Wirkstoffe transportieren können oder auf andere Weise die Wirkstoffpermeation durch die Poren ermöglichen können, nachdem die Penetriermittel in die Poren eingedrungen sind, wobei die Wirkstoffe, die mit den genannten Penetriermitteln assoziiert sind, Corticosteroide, insbesondere Glukocorticoide oder Mineralocorticosteroide, sind,
dadurch gekennzeichnet, dass der relative Gehalt an Corticosteroiden über 0.1 Gew.-% relativ zu der Gesamttrockenmasse der Formulierung beträgt und
die Formulierung wenigstens ein Antioxidationsmittel in einer Menge enthält, die die Erhöhung des Oxidationsindex auf weniger als 100 % in 6 Monaten reduziert.

2. Formulierung gemäß Anspruch 1,
dadurch gekennzeichnet, dass die Formulierung wenigstens einen Konsistenzbildner in einer Menge umfasst, die die Formulierungsviskosität über die einer nicht verdickten entsprechenden Formulierung auf maximal 5 Ns/m^2 erhöht, so dass die Verteilung über und das Verbleiben auf der Anwendungsfläche ermöglicht wird und/oder wenigstens ein Mikrobiozid in einer Menge, die die Keimzahl von 1 Millionen Keimen, die pro Gramm Gesamtmasse der Formulierung zugegeben wurden, nach einem Zeitraum von 4 Tagen auf weniger als 100 im Falle von aeroben Bakterien, auf weniger als 10 im Falle von Enterobakterien und auf weniger als 1 im Falle von Pseudomonas aeruginosa oder Staphilococcus aureus, reduziert.

3. Formulierung gemäß Anspruch 2,
dadurch gekennzeichnet, dass der genannte wenigstens eine Konsistenzbildner in einer Menge zugegeben wird, die die Formulierungsviskosität auf bis zu 1 Ns/m^2 und mehr bevorzugt auf 0.2 Ns/m^2 erhöht.

4. Formulierung gemäß den Ansprüchen 1 bis 3,
dadurch gekennzeichnet, dass das genannte wenigstens eine Antioxidationsmittel in einer Menge zugegeben wird, die die Erhöhung des Oxidationsindex auf weniger als 100 % in 12 Monaten und mehr bevorzugt auf weniger als 50 % in 12 Monaten reduziert.

5. Formulierung gemäß den Ansprüchen 2 bis 4,
dadurch gekennzeichnet, dass das genannte wenigstens eine Mikrobiozid in einer Menge zugegeben wird, die die Keimzahl von 1 Million Keimen, die pro Gramm Gesamtmasse der Formulierung zugegeben wurden, nach einem Zeitraum von 3 Tagen und mehr bevorzugt in einem Zeitraum von 1 Tag auf weniger als 100 im Falle von aeroben Bakterien, auf weniger als 10 im Falle von Enterobakterien und auf weniger als 1 im Falle von Pseudomonas aeruginosa oder Staphilococcus aureus reduziert.

6. Formulierung gemäß einem der Ansprüche 2 bis 5,
dadurch gekennzeichnet, dass der Konsistenzbildner ausgewählt ist aus pharmazeutisch verträglichen hydrophilen Polymeren, wie teilweise veretherten Cellulosederivaten umfassend Carboxymethyl -, Hydroxyethyl-, Hydroxypropyl-, Hydroxypropylmethyl- oder Methylcellulose; vollständig synthetische hydrophile Polymere umfassend Polyacrylate, Polymethacrylate, Poly(hydroxyethyl)-, Poly(hydroxypropyl)-, Poly(hydroxypropylmethyl)methacrylat, Polyacrylnitril, Methylallylsulphonat, Polyethylene, Polyoxyethylene, Polyethylenglycole, Polyethylenglycollactid, Polyethylenglycoldiacrylat, Polyvinylpyrrolidon, Polyvinylalkohole, Poly(propylmethacrylamid), Poly(propylenfumarat-co-ethylenglycol), Poloxamere, Polyaspartamid, (Hydrazin-quervernetzte) Hyaluronsäure, Silikon; Naturgummis umfassend Alginate, Carrageenan, Guar Gum, Gelatine, Tragant, (amidiertes) Pectin, Xanthan, Chitosancollagen, Agarose; Mischungen und weitere Derivate oder Copolymere davon und/oder andere pharmazeutisch oder wenigstens biologisch verträgliche Polymere.

7. Formulierung gemäß Anspruch 6,
dadurch gekennzeichnet, dass der Polymergewichtsanteil in dem Bereich zwischen 0.05 % und 10 %, mehr bevorzugt in dem Bereich zwischen 0.1 % und 5 %, noch mehr bevorzugt in dem Bereich zwischen 0.25 % und 3.5 % und am meisten bevorzugt in dem Bereich zwischen 0.5 % und 2 % liegt.

8. Formulierung gemäß einem der Ansprüche 1 bis 7,
dadurch gekennzeichnet, dass das Antioxidationsmittel ausgewählt ist aus synthetischen phenolischen Antioxidationsmitteln wie butyliertem Hydroxyanisol (BHA), butyliertem Hydroxytoluol (BHT) und Di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), tertiärem Butylhydrochinon (TBHQ), Propylgallat (PG), 1-O-Hexyl-2,3,5-trimethylhydrochinon (HTHQ); aromatischen Aminen, umfassend Diphenylamin, p-Alkylthio-o-anisidin, Ethylendiamin-Derivaten, Carbazol und Tetrahydroindenoindol; Phenolen und Phenolcarbonsäuren, umfassend Guajacol, Hydrochinon, Vanillin, Gallussäure und ihre Ester, Protocatechusäure, Chinasäure, Syringasäure, Ellagsäure, Salicylsäure, Nordihydroguajaretsäure (NDGA) und Eugenol; Tocopherole und ihre Derivate, umfassend Tocopherylacylat, -laurat, -myristat, -palmitat, -oleat, -linoleat oder andere geeignete, Tocopheryllipoat, Tocopheryl-POE-succinat; Trolox und entsprechende Amid- und Thiocarboxamid-Analoga; Ascorbinsäure und ihre Salze, Isoascorbat, (2- oder 3- oder 6-)o-Alkylascorbinsäuren, Ascorbinsäureester umfassend 6-o-Lauroyl-, Myristoyl-, Palmitoyl-, Oleoyl- oder Linoleoyl-L-ascorbinsäure; nicht-steroidale antiinflammatorische Arzneimittel (NSAIDs) wie Indomethacin, Diclofenac, Mefenaminsäure, Flufenaminsäure, Phenylbutazon, Oxyphenbutazonacetylsalicylsäure, Naproxen, Diflunisal, Ibuprofen, Ketoprofen, Piroxicam, Penicillamin, Penicillamindisulfid, Primaquin, Chinacrin, Chloroquin, Hydroxychloroquin, Azathioprin, Phenobarbital, Acetaminophen; Aminosalicylsäuren und Derivate; Methotrexat, Probucol, Antiarrhythmika, umfassend Amiodaron, Aprindin und Asocainol; Ambroxol, Tamoxifen, β-Hydroxytamoxifen; Calcium-Antagonisten, umfassend Nifedipin, Nisoldipin, Nimodipin, Nicardipin und Nilvadipin, Betarezeptorblocker umfassend Atenolol, Propranolol und Nebivolol; Natriumhydrogensulfit, Natriumdisulfit, Thioharnstoff; Chelatbildner wie EDTA, GDTA, Desferral; verschiedene endogene Abwehrsysteme wie Transferrin, Lactoferrin, Ferritin, Cearuloplasmin, Haptoglobion, Haemopexin, Albumin, Glucose, Ubiquinol-10; enzymatische Antioxidantien wie Superoxid-Dismutase und Metallkomplexe mit einer ähnlichen Aktivität, umfassend Catalase, Glutathionperoxidase und weniger komplexe Moleküle wie beta-Carotin, Bilirubin, Harnsäure; Flavonoide umfassend Flavone, Flavonole, Flavonone, Flavanonale und Chacone, Anthocyanine; N-Acetylcystein, Mesna, Glutathion, Thiohistidin-Derivate, Triazole; Tannine, Zimtsäure, Hydroxyzimtsäuren und ihre Ester, umfassend Cumarsäuren und Ester, Kaffeesäure und ihre Ester, Ferulasäure, (Iso-) Chlorogensäure und Sinapinsäure; Gewürzextrakte, umfassend Gewürzextrakte aus Gewürznelke, Zimt, Salbei, Rosmarin, Muskatblüte, Oregano, Piment and Muskatnuß; Carnosinsäure, Carnosol, Carsolsäure; Rosmarinsäure, Rosmaridiphenol, Gentisinsäure, Ferulasäure; Hafermehlextrakte, wie Avenanthramid 1 und 2; Thioether, Dithioether, Sulphoxide, Tetralkylthiuramdisulfide; Phytinsäure, Steroidderivate, umfassend U74006F; Tryptophan-Meta-

bolite, umfassend 3-Hydroxykynurenin und 3-Hydroxyanthranilsäure; und Organochalcogenide.

9. Formulierung gemäß Anspruch 8,
dadurch gekennzeichnet, dass die Konzentration von BHA oder BHT zwischen 0.001 und 2 Gew.-%, mehr bevorzugt zwischen 0.0025 und 0.2 Gew.-% und am meisten bevorzugt zwischen 0.005 und 0.02 Gew.-% beträgt, von TBHQ und PG zwischen 0.001 und 2 Gew.-%, mehr bevorzugt zwischen 0.005 und 0.2 Gew.-% und am meisten bevorzugt zwischen 0.01 und 0.02 Gew.-% beträgt, von Tocopherol zwischen 0.005 und 5 Gew.-%, mehr bevorzugt zwischen 0.01 und 0.5 Gew.-% und am meisten bevorzugt zwischen 0.05 und 0.075 Gew.-% beträgt, von Ascorbinsäureestem zwischen 0.001 und 5, mehr bevorzugt zwischen 0.005 und 0.5 und am meisten bevorzugt zwischen 0.01 und 0.15 Gew.-% beträgt, von Ascorbinsäure zwischen 0.001 und 5, mehr bevorzugt zwischen 0.005 und 0.5 Gew.-% und am meisten bevorzugt zwischen 0.01 und 0.1 Gew.-% beträgt, von Natriumhydrogensulfit oder Natriumdisulfit zwischen 0.001 und 5, mehr bevorzugt zwischen 0.005 und 0.5 Gew.-% und am meisten bevorzugt zwischen 0.01 - 0.15 Gew.-% beträgt, von Thioharnstoff zwischen 0.0001 und 2 Gew.-%, mehr bevorzugt zwischen 0.0005 und 0.2 und am meisten bevorzugt zwischen 0.001 - 0.01 Gew.-%, am typischsten 0.005 Gew.-% beträt, von Cystein zwischen 0.01 und 5, mehr bevorzugt zwischen 0.05 und 2 Gew.-% und am meisten bevorzugt zwischen 0.1 und 1.0 Gew.-%, am typischsten 0.5 Gew.-% beträgt, von Monothioglycerol zwischen 0.01 und 5 Gew.-%, mehr bevorzugt zwischen 0.5 und 2 Gew.-% und am meisten bevorzugt zwischen 0.1 - 1.0 Gew.-%, am typischsten 0.5 Gew.-% beträgt, von NDGA zwischen 0.0005 - 2 Gew.-%, mehr bevorzugt zwischen 0.001 - 0.2 Gew.-% und am meisten bevorzugt zwischen 0.005 - 0.02 Gew.-%, am typischsten 0.01 Gew.-% beträgt, von Glutahion zwischen 0.005 und 5 Gew.-%, mehr bevorzugt zwischen 0.01 und 0.5 Gew.-% und am meisten bevorzugt zwischen 0.05 und 0.2 Gew.-%, am typischsten 0.1 Gew.-% beträgt, von EDTA zwischen 0.001 und 5 Gew.-%, noch mehr bevorzugt zwischen 0.005 und 0.5 Gew.-% und am meisten bevorzugt zwischen 0.01 und 0.2 Gew.-%, am typischsten zwischen 0.05 und 0.975 Gew.-% beträgt, von Zitronensäure zwischen 0.001 und 5 Gew.-%, noch mehr bevorzugt zwischen 0.005 und 3 Gew.-% und am meisten bevorzugt zwischen 0.01 - 0.2, am typischsten zwischen 0.3 und 2 Gew.-% beträgt.

10. Formulierung gemäß einem der Ansprüche 2 bis 9,
dadurch gekennzeichnet, dass das Mikrobiozid ausgewählt ist aus kurzkettigen Alkoholen, umfassend Ethyl- und Isopropylalkohol, Chlorbutanol, Benzylalkohol, Chlorbenzylakohol, Dichlorbenzylalkohol, Hexachlorophen; phenolischen Verbindungen wie Cresol, 4-Chlor-m-cresol, p-Chlor-m-xylenol, Dichlorophene, Hexachlorophene, Povidon-Iod; Parabene, insbesondere Alkylparabene wie Methyl-, Ethyl-, Propyl- oder Butylparaben, Benzylparaben; Säuren wie Sorbinsäure, Benzoesäure und ihre Salts; quartäre Ammoniumverbindungen wie Alkoniumsalze, z.B. ein Bromid, Benzalkoniumsalze wie ein Chlorid oder ein Bromid, Cetrimoniumsalze, z.B. ein Bromid, Phenoalkeciniumsalze wie Phenododeciniumbromid, Cetylpyridiniumchlorid und andere Salze; Quecksilberverbindungen wie Phenylquecksilberacetat, -borat, oder -nitrat, Thiomersal, Chlorhexidin oder sein Gluconat, oder jede antibiotisch wirksame Verbindung biologischen Ursprungs oder jede Mischung davon.

11. Formulierung gemäß Anspruch 10,
dadurch gekennzeichnet, dass die Mengenkonzentration kurzkettiger Alkohole im Falle von Ethyl-, Propyl-, Butyl- oder Benzylalkohol bis zu 10 Gew.-%, mehr bevorzugt bis zu 5 Gew.-% beträgt und am meisten bevorzugt im Bereich zwischen 0.5 - 3 Gew.-% liegt, im Falle von Chlorbutanol im Bereich zwischen 0.3 - 0.6 Gew.-% liegt; die Mengenkonzentration an Parabenen, insbesondere im Falle von Methylparaben im Bereich zwischen 0.05 - 0.2 Gew.-% liegt und im Falle von Propylparaben im Bereich zwischen 0.002 - 0.02 Gew.-% liegt; die Mengenkonzentration an Sorbinsäure im Bereich zwischen 0.05 - 0.2 Gew.-% liegt und im Falle von Benzoesäure im Bereich zwischen 0.1 - 0.5 Gew.-% liegt; die Mengenkonzentration an Phenolen, Triclosan, im Bereich zwischen 0.1 - 0.3 Gew.-% liegt und die Mengenkonzentration an Chlorhexidin im Bereich zwischen 0.01 - 0.05 Gew.-% liegt.

12. Formulierung gemäß einem der vorangegangenen Ansprüche,
dadurch gekennzeichnet, dass das Corticosteroid ausgewählt ist aus Alclonetasondipropionat, Amcinonid, Beclomethasondipropionat, Betamethason, Betamethason-17-valerat, Betamethason-17,21-divalerat, Betamethason-21-acetat, Betamethason-21-buytrat, Betamethason-21-propionat, Betamethason-21-valerat, Betamethasonbenzoat, Betamethasondipropionat, Betamethasonvalerat, Budesonid, Clobetasolpropionat, Clobetasonbutyrat, Cortexolon, Corticosteron, Cortison, Cortison-17-acetat, 21-Deoxybetamethason, 21-Deoxybetamethason-17-propionat, Deoxycorticosteron, Desonid, Desoxymethason, Dexamethason, Diflorasondiacetat, Diflucortolonvalerat, Fluclorolonеacetonid, Flumethasonpivalat, Fluocinolonacetonid, Fluocinonid, Fluocortin-Butyl, Fluocortolon, 9-alpha-Fluorcortison, 9-alpha-Fluorhydrocortison, 9-alpha-Fluorprednisolon, Fluprednidenacetat, Flurandrenolon, Halcinonid, Hydrocortison, Hydrocortison-17-acetat, Hydrocortison-17-butyrat, Hydrocortison-17-propionat, Hydrocortison-17-valerat, Hydrocortison-21-acetat, Hydrocortison-21-butyrat, Hydrocortison-21-propionat,

Hydrocortison-21-valerat, 17-alpha-Hydroxyprogesteron, Methylprednisolonacetat, Mometasonfuroat, Prednisolon, Prednison, Prednison-17-acetat, Prednison-17-valerat, Progesteron, Triamcinolon, Triamcinolonacetonid.

13. Formulierung gemäß einem der vorangegangenen Ansprüche,
dadurch gekennzeichnet, dass die Penetriermittel in der Form von fluiden Tröpfchen, die von einer membranartigen Schicht aus einer oder mehreren Lagen umgeben ist, in einer polaren Flüssigkeit suspendiert oder dispergiert werden, wobei die genannte Schicht wenigstens zwei Arten oder Formen amphiphiler Substanzen mit einer Neigung zu aggregieren umfasst, vorausgesetzt, dass die genannten wenigstens zwei Substanzen sich mindestens um einen Faktor von 10 in der Löslichkeit in der genannten Flüssigkeit unterscheiden oder, andererseits, dass die genannten Substanzen, wenn sie in der Form von Homoaggregaten bezüglich der löslicheren Substanz oder von Heteroaggregaten bezüglich jeder Kombination der beiden genannten Substanzen vorliegen, einen bevorzugten durchschnittlichen Durchmesser aufweisen, der kleiner ist als der Durchmesser der Homoaggregate, die nur die weniger lösliche Substanz enthalten; oder auch vorausgesetzt, dass das Vorliegen der löslicheren Substanz die durchschnittliche elastische Energie der membranartigen Schicht in der Umgebung von thermaler Energie erniedrigt.

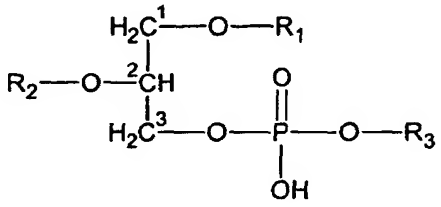
14. Formulierung gemäß Anspruch 13,
dadurch gekennzeichnet, dass die löslichere Substanz dazu neigt, die Tröpfchen zu solubilisieren und der Gehalt dieser Substanz bis zu 99 Mol-% der Solubilisierungskonzentration beträgt oder andererseits bis zu 99 Mol-% der Sättigungskonzentration in dem nicht solubilisierten Tröpfchen entspricht, je nach dem welcher höher ist.

15. Formulierung gemäß Anspruch 14,
dadurch gekennzeichnet, dass der Gehalt an löslicherer Substanz unter 50 %, insbesondere unter 40 % und am meisten bevorzugt unter 30 % der genannten Solubilisierungskonzentration der genannten Substanz beträgt.

16. Formulierung gemäß Anspruch 14,
dadurch gekennzeichnet, dass der Gehalt der löslicheren Substanz unter 80 %, bevorzugt unter 65 % und am meisten bevorzugt unter 50 % der genannten Sättigungskonzentration der genannten Substanz in dem Tröpfchen beträgt.

17. Formulierung gemäß einem der Ansprüche 13 bis 16,
dadurch gekennzeichnet, dass die weniger lösliche der aggregierenden Substanzen ein Lipid oder lipidähnliches Material ist, insbesondere ein polares Lipid, wohingegen die Substanz, die in der Suspensionsflüssigkeit löslicher ist und welche die Tröpfchenadaptabilität erhöht, zu den oberflächenaktiven Stoffen gehört oder anderweitig oberflächenaktive Eigenschaften aufweist.

18. Formulierung gemäß Anspruch 17,
dadurch gekennzeichnet, dass das Lipid oder lipidähnliche Material ein Lipid oder Lipoid aus einer biologischen Quelle oder ein entsprechendes synthetisches Lipid oder eine seiner Modifikationen ist, wobei das genannte Lipid bevorzugt zu der Klasse der reinen Phospholipide mit der chemischen Formel



gehört, in der R_1 und R_2 eine aliphatische Kette, typischerweise ein C_{10-20}-Acyl oder -Alkyl oder teilweise ungesättigter Fettsäurerest ist, insbesondere eine Oleoyl-, Palmitoeloyl-, Elaidoyl-, Linoleyl-, Linolenyl-, Linolenoyl-, Arachidoyl-, Vaccinyl-, Lauroyl-, Myristoyl-, Palmitoyl-, oder Stearoyl-Kette ist; und in der R_3 Wasserstoff, 2-Trimethylamino-1-ethyl, 2-Amino-1-ethyl, C_{1-4}-Alkyl, Carboxy-substituiertes C_{1-5}-Alkyl, Hydroxy-substituiertes C_{2-5}-Alkyl, Carboxy- und Hydroxy-substituiertes C_{2-5}-Alkyl oder Carboxy- und Aminosubstituiertes C_{2-5}-Alkyl ist, Inositol, Sphingosin oder Salze der genannten Substanzen, wobei das genannte Lipid auch Glyceride, Isoprenoid-Lipide, Steroide, Sterine oder Sterole, Schwefel oder Kohlenwasserstoff enthaltende Lipide oder andere Doppelschicht bildende Lipide umfaßt, insbesondere halb protonierte fluide Fettsäuren, wobei das genannte Lipid ausgewählt ist

aus der Gruppe umfassend Phosphatidylcholine, Phosphatidylethanolamine, Phosphatidylglycerole, Phosphatidylinositole, Phosphatidsäuren, Phosphatidylserine, Sphingomyeline oder andere Sphingophospholipide, Glycosphingolipide (umfassend Cerebroside, Ceramidpolyhexoside, Sulphatide, Sphingoplasmalogene), Ganglioside und andere Glycolipide oder synthetische Lipide, insbesondere mit entsprechenden Sphingosin-Derivaten, oder andere Glycolipide, wobei zwei gleiche oder unterschiedliche Ketten über Ester-Gruppen mit dem Rückgrat verbunden sein können (wie in Diacyl- und Dialkenoyl-Verbindungen) oder mit Etherbindungen an dem Rückgrat angebracht sein können wie in Dialkyl-Lipiden.

19. Formulierung gemäß Anspruch 17,
dadurch gekennzeichnet, dass die oberflächenaktive Substanz oder das einer oberflächenaktiven Substanz ähnliche Material eine nichtionische, eine zwitterionische, eine anionische oder eine kationische oberflächenaktive Substanz ist, insbesondere eine Fettsäure oder ein Fettalkohol, ein Alkyltri/di/methylammoniumsalz, ein Alkylsulfatsalz, ein einwertiges Cholatsalz, Deoxycholat, Glycocholat, Glycodeoxycholat, Taurodeoxycholat, Taurocholat, ein Acyl- oder Alkanoyldimethylaminoxid, insbesondere ein Dodecyldimethylaminoxid, ein Alkyl- oder Alkanoyl-N-methylglucamid, N-Alkyl-N,N-dimethylglycin, 3-(Acyldimethylammonio)alkylsulphonat, N-Acylsulphobetain, ein Polyethylenglycoloctylphenylether, insbesondere ein Nonaethylenglycoloctylphenylether, ein Polyethylenacylether, insbesondere ein Nonaethylendodecylether, ein Polyethylenglycolisoacylether, insbesondere ein Octaethylenglycolisotridecylether, Polyethylenacylether, insbesondere Octaethylendodecylether, Polyethylenglycolsorbitanacylester wie Polyethylenglykol-20-monolaurat (Tween 20) oder Polyethylenglykol-20-sorbitanmonooleat (Tween 80), ein Polyhydroxyethyleneacylether, insbesondere Polyhydroxyethylenlauryl, -myristoyl, -cetylstearyl, oder -oleoylether wie in Polyhydroxyethylen-4 oder 6- oder 8- oder 10- oder 12-, etc., -laurylether (wie in der Brij-Serie), oder in dem entsprechenden Ester, z.B. des Polyhydroxyethylen-8-stearat (Myrj 45), -laurat oder —oleate-Typs, oder in polyethoxyliertem Castoröl 40, ein Sorbitanmonoalkylat (z.B. in Arlacel oder Span), insbesondere Sorbitanmonolaurat, ein Acyl- oder Alkanoyl-N-methylglucamid, insbesondere in Decanoyl- oder Dodecanoyl-N-methylglucamid, ein Alkylsulfat (Salz), z.B. in Lauryl- oder Oleoylsulfat, Natriumdeoxycholat, Natriumglycodeoxycholat, Natriumoleat, Natriumtaurat, ein Fettsäuresalz wie Natriumelaidat, Natriumlinoleat, Natriumlaurat, ein Lysophospholipid, wie n-Octadecylen(=-oleoyl)-glycerophosphatidsäure, -phosphorylglycerol, oder -phosphorylserin, n-Acyl-, z.B. Lauryl- oder Oleoylglycerophosphatidsäure, -phosphorylglycerol, or -phosphorylserin, n-Tetradecylglycerophosphatidsäure, -phosphorylglycerol, oder -phosphorylserin, ein entsprechendes Palmitoeloyl-, Elaidoyl-, Vaccenyllysophospholipid oder ein entsprechendes kurzkettiges oder ein sonstiges oberflächenaktives Polypeptid.

20. Formulierung gemäß einem der Ansprüche 13 bis 19,
dadurch gekennzeichnet, dass der durchschnittliche Durchmesser des Penetriermittels zwischen 30 nm und 500 nm, bevorzugt zwischen 40 nm und 250 nm, noch mehr bevorzugt zwischen 50 nm und 200 nm und am meisten bevorzugt zwischen 60 nm und 150 nm beträgt.

21. Formulierung gemäß einem der Ansprüche 13 bis 19,
dadurch gekennzeichnet, dass der durchschnittliche Durchmesser des Penetriermittels 2 bis 25 mal größer als der durchschnittliche Durchmesser der Poren der Barriere ist, bevorzugt zwischen 2.25 und 15 mal größer, noch mehr bevorzugt zwischen 2.5 und 8 mal größer und am meisten bevorzugt zwischen 3 und 6 mal größer als der genannte durchschnittliche Porendurchmesser.

22. Formulierung gemäß einem der Ansprüche 13 bis 21,
dadurch gekennzeichnet, dass das Trockengewicht aller Trägertröpfchen in einer Formulierung zur Verwendung auf menschlicher oder tierischer Haut 0.01 Gewichts-% (Gew.-%) bis 40 Gew.-% der Gesamtformulierungsmasse, insbesondere zwischen 0.1 Gew.-% und 30 Gew.-%, besonders bevorzugt zwischen 0.5 Gew.-% und 20 Gew.-% und am meisten bevorzugt zwischen 1 Gew.-% und 10 Gew.-% beträgt.

23. Formulierung gemäß einem der Ansprüche 13 bis 21,
dadurch gekennzeichnet, dass das Trockengewicht aller Trägertröpfchen in einer Formulierung zur Verwendung auf menschlicher oder tierischer Schleimhaut 0.0001 Gew.-% bis 30 Gew.-% der Gesamtformulierungsmasse beträgt.

24. Formulierung gemäß einem der Ansprüche 1 bis 23,
dadurch gekennzeichnet, dass der pH der Trägersuspension zwischen 4 und 10, bevorzugt zwischen 5 und 9 und noch öfter bis zu 8.5 beträgt wie es zur Maximierung der Formulierungsstabilität erforderlich ist.

25. Verfahren zur Herstellung einer Formulierung zur nichtinvasiven Anwendung in vivo gemäß einem der vorange-

gangen Ansprüche,
dadurch gekennzeichnet, dass die Penetriermittel, die zur Assoziation und/oder Inkorporierung der genannten Wirkstoffmoleküle in der Lage sind, aus wenigstens einer amphiphilen Substanz, wengistens einem polaren Fluid, wenigstens einer randaktiven Substanz oder oberflächenaktiven Substanz, wenigstens einem Corticosteroid in einer Menge von mehr als 0.1 Gew.-% basierend auf der Gesamttrockenmasse der Formulierung und gegebenenfalls anderen üblichen Inhaltsstoffen, die zusammen die genannte Formulierung bilden, gebildet werden.

26. Verfahren nach Anspruch 25,
dadurch gekennzeichnet, dass wenigstens eine randaktive Substanz oder oberflächenaktive Substanz, wenigstens eine amphiphile Substanz, wenigstens ein hydrophiles Fluid und der Wirkstoff zur Bildung einer Lösung gelöst werden und, falls erforderlich, getrennt gemischt werden, wobei die resultierenden (teilweisen) Mischungen oder Lösungen anschließend kombiniert werden, um daraufhin, bevorzugt durch die Wirkung mechanischer Energie wie Schütteln, Rühren, Vibrieren, Homogenisieren, Ultraschall, Scheren, Einfrieren und Auftauen oder Filtration unter Verwendung üblichen Antriebsdrucks, die Bildung der Penetriermittel, die mit dem Wirkstoff assozieren und/oder diesen inkorporieren, zu induzieren.

27. Verfahren nach den Ansprüchen 25 oder 26,
dadurch gekennzeichnet, dass die genannten amphiphilen Substanzen entweder als solche verwendet werden oder in einem physiologisch verträglichen polaren Fluid, welches Wasser oder mit Wasser mischbar sein kann oder in einem Lösungsvermittler zusammen mit einer polaren Lösung gelöst werden.

28. Verfahren nach den Ansprüchen 25 oder 26,
dadurch gekennzeichnet, dass die genannten amphiphilen Substanzen in hochflüchtigen Alkoholen gelöst werden, insbesondere Ethanol, oder in pharmazeutisch verträglichen organischen Lösungsmitteln, die anschließend, insbesondere durch Verdampfen entfernt werden, bevor die Endzubereitung hergestellt wird.

29. Verfahren wie in den Ansprüchen 27 oder 28 beansprucht,
dadurch gekennzeichnet, dass die polare Lösung wenigstens eine randaktive Substanz oder oberflächenaktive Substanz enthält.

30. Verfahren gemäß einem der Ansprüche 25 bis 29,
dadurch gekennzeichnet, dass die Bildung der genannten Penetriermittel durch die Zugabe der erforderlichen Substanzen in eine fluide Phase, Verdampfen aus einer reversen Phase, durch Injektion oder Dialyse, falls notwendig unter dem Einfluss von mechanischer Beanspruchung wie Schütteln, Rühren, insbesondere Rühren unter hoher Geschwindigkeit, Vibrieren, Homogenisieren, Ultraschall, Scheren, Einfrieren und Auftauen oder Filtration unter Verwendung eines üblichen, insbesondere geringen (1 MPa) oder mittleren (bis zu 10 MPa) Antriebsdruck induziert wird.

31. Verfahren nach Anspruch 30,
dadurch gekennzeichnet, dass die Bildung der genannten Penetriermittel durch Filtration induziert wird, wobei das Filtermaterial Porengrößen zwischen 0.01 μm und 0.8 μm, bevorzugt zwischen 0.02 μm und 0.3 μm und am meisten bevorzugt zwischen 0.05 μm und 0.15 μm aufweisen, wobei mehrere Filter nacheinander oder parallel verwendet werden können.

32. Verfahren gemäß einem der Ansprüche 25 bis 31,
dadurch gekennzeichnet, dass die genannten Wirkstoffe und Penetriermittel nach der Bildung der genannten Penetriermittel, z. B. nach der Injektion einer Lösung des Arzneimittels in ein pharmazeutisch verträgliches Fluid wie Ethanol, 1-und 2-Propanol, Benzylalkohol, Propylenglykol, Polyethylenglykol (Molekulargewicht: 200 - 400 D) oder Glycerol in ein Suspensionsmedium, zumindest teilweise zur Assoziation gebracht werden, wobei die genannten Penetriermittel unter Verwendung der entsprechenden oder einer anderen geeigneten Herstellungsmethode oder simultan mit der Arzneimittelinjektion gebildet werden, falls erforderlich unter Verwendung einer Co-Lösung des Arzneimittels und wenigstens einigen Penetriermittelinhaltsstoffen.

33. Verfahren gemäß einem der Ansprüche 25 bis 32,
dadurch gekennzeichnet, dass die genannten Penetriermittel, mit denen die Wirkstoffmoleküle assoziiert sind und/oder in die der Wirkstoff inkorporiert ist, unmittelbar vor der Anwendung der Formulierung, falls zweckdienlich aus einem geeigneten Konzentrat oder Lyophylisat, hergestellt werden.

34. Formulierung gemäß einem der Ansprüche 1 bis 24,
dadurch gekennzeichnet, dass der Gehalt an Corticosteroiden zwischen 0.1 Gew.-% und 20 Gew.-%, mehr bevorzugt zwischen 0.25 Gew.-% und 10 Gew.-% und noch mehr bevorzugt zwischen 0.5 Gew.-% und 5 Gew.-% relativ zu der Gesamttrockenmasse der arzneimittelbeladenen Träger beträgt.

35. Formulierung gemäß Anspruch 34,
dadurch gekennzeichnet, dass der relative Gehalt an Corticosteroiden im Falle von Triamcinolon oder einem seiner Derivate wie Acetonid unter 2 -Gew.-% relativ zur Gesamttrockenmasse der arzneimittelbeladenen Träger beträgt, noch mehr bevorzugt unterhalb 1 Gew.-% und am meisten bevorzugt weniger als 0.5 Gew.-% beträgt.

36. Formulierung gemäß Anspruch 34,
dadurch gekennzeichnet, dass der relative Gehalt an Corticosteroiden im Falle von Hydrocortison oder einem seiner Derivate unter 20 Gew.-% relativ zur Gesamttrockenmasse der arzneimittelbeladenen Träger, noch mehr bevorzugt unter 12.5 Gew.-% und am meisten bevorzugt unter 5 Gew.-% beträgt.

37. Formulierung gemäß Anspruch 34,
dadurch gekennzeichnet, dass der relative Gehalt an Corticosteroiden im Falle von Dexamethason oder einem seiner Derivate unter 15 Gew.-% relativ zur Gesamttrockenmasse der arzneimittelbeladenen Träger, noch mehr bevorzugt unter 10 Gew.-% und am meisten bevorzugt unter 5 Gew.-% beträgt.

38. Formulierung gemäß Anspruch 34,
dadurch gekennzeichnet, dass der relative Gehalt an Corticosteroiden im Falle von Clobetasol oder einem seiner Derivate wie dem Propionat unter 15 Gew.-% relativ zur Gesamttrockenmasse der arzneimittelbeladenen Träger, noch mehr bevorzugt unter 10 Gew.-% und am meisten bevorzugt unter 5 Gew.-% beträgt.

39. Formulierung gemäß den Ansprüchen 34 bis 38,
dadurch gekennzeichnet, dass der Gehalt an dem genannten Corticosteroid unterhalb des Sättigungsmaximum liegt, das definiert ist als der Gehalt an Corticosteroid, an dem das Corticosteroid in oder außerhalb des Trägers zu kristallisieren beginnt.

40. Formulierung gemäß den Ansprüchen 1 bis 24 und 34 bis 37,
dadurch gekennzeichnet, dass zur Beschleunigung der Arzneimittelwirkung ein Permeationsverstärker zugegeben wird.

41. Formulierung gemäß Anspruch 40,
dadurch gekennzeichnet, dass der Permeationsverstärker ausgewählt ist aus 1-Acylazacycloheptan-2-onen (Azonen), 1-Acylglucosiden, 1-Acylpolyoxyethylenen, 1-Acylsacchariden, 2-n-Acylcyclohexanonen, 2-n-Acyl-1,3-dioxolanen (SEPA), 1,2,3-Triacylglycerolen, 1-Alkanolen, 1-Alkansäuren, 1-Alkylacetaten, 1-Alkylaminen, 1-Alkyl-n-alkylpolyoxyethylenen, 1-Alkylalkylaten, n-Alkyl-beta-D-thioglucosiden, 1-Alkylglyceriden, 1-Alkylpropylenglycolen, 1-Alkylpolyoxyethylenen, (1-Alkyl-)2-pyrrolidonen, Alkylacetoacetaten, Alkylenglycolen, Alkylmethylsulfoxiden (Alkyl-DMSO), Alkylpropionaten, Alkylsulfaten, Diacylsuccinaten, Diacyl-N,N-dimethylaminoacetaten (DDAA), Diacyl-N,N-dimethylaminoisopropionaten (DDAIP), Phenylalkylaminen.

42. Formulierung gemäß Anspruch 41,
dadurch gekennzeichnet, dass der Mengenkonzentrationsbereich der verwendeten Verstärker bis zu 5 % für 1-Caprylpropylenglykol, 6 - 10 % für 1-[2-(Decylthio)ethyl]azacyclopentan-2-on (=HPE-101), < 10 % für 1-Dodecanol, < 10 % für 1-Dodecylazacycloheptan-2-on (=Azon), etwa 10 % für 2-n-Nonyl-1,3-dioxolan (SEPA), < 10 % für 2-n-Octylcyclohexanon, bis zu 20 % für DMSO und zwischen 5 % und 40 % für Ethanol, mindestens 10 % für Ethylenglykol, bis zu 30 % für Ethylacetat, 5 - 50 % für Glycerol, bis zu 75 % für Isopropanol, 1 - 20 % für Isopropylmyristat, zwischen 1 und 20 % für Oleinsäure und Oleylalkohol, etwa 1 % für Oleylpolyoxyethylenether, wenigstens 10 % für Propylenglykol beträgt.

43. Formulierung gemäß den Ansprüchen 1 bis 24 und 34 bis 42,
dadurch gekennzeichnet, dass das genannte Corticosteroid in einer Menge zugegeben wird, die es ermöglicht, dass die Formulierung entsprechend einer Flächendosis ausgedrückt durch die pro Flächeneinheit aufgetragene Gesamttrockenmasse an Penetriermittel von zwischen 0.1 mg cm^{-2} und 15 mg cm^{-2}, mehr bevorzugt zwischen 0.5 mg cm^{-2} und 10 mg cm^{-2}, besonders bevorzugt zwischen 0.75 mg cm^{-2} und 5 mg cm^{-2} und am meisten bevorzugt zwischen 1 mg cm^{-2} und 2.5 mg cm^{-2} aufgetragen wird, falls das genannte Corticosteroid eine therapeu-

tische Wirkung in den tiefen subkutanen, z. B. Muskel- oder Gelenksgewebe oder in sonstigen entfernten Gewebe umfassend den ganzen Körper, ausüben soll.

44. Formulierung gemäß den Ansprüchen 1 bis 24 und 34 bis 42,
dadurch gekennzeichnet, dass das genannte Corticosteroid in einer Menge zugegeben wird, die es ermöglicht, dass die Formulierung in einer Flächendosis ausgedrückt durch die pro Flächeneinheit aufgetragene Gesamttrokkenmasse an Penetriermittel von zwischen 1 μg cm^{-2} und 250 μg cm^{-2}, mehr bevorzugt zwischen 2.5 und 100 μg cm^{-2}, noch mehr bevorzugt zwischen 5 μg cm^{-2} und 50 μg cm^{-2} und am meisten bevorzugt zwischen 7.5 μg cm^{-2} und 20 μg cm^{-2} aufgetragen wird, falls das genannte Corticosteroid eine hauptsächlich lokale, d. h. eher oberflächliche als systemische therapeutische Wirkung ausüben soll.

45. Formulierung gemäß den Ansprüchen 1 bis 24 und 34 bis 44,
dadurch gekennzeichnet, dass die Konsistenz und, falls nötig andere Eigenschaften der Formulierung geeignet ausgewählt werden, so dass Aufsprühen, Aufschmieren, Aufrollen oder Aufwischen der Formulierung auf die Auftragungsfläche, je nach Eignung insbesondere unter Verwendung eines Sprays, Spenders, einer Rolle oder eines Schwammes möglich sind.

46. Verwendung der Formulierungen gemäß einem der vorangegangenen Ansprüche zur Herstellung eines Medikaments für die nichtinvasive Anwendung von Corticosteroiden,
dadurch gekennzeichnet, dass die Flächendosis ausgedrückt durch die pro Flächeneinheit aufgetragene Gesamttrockenmasse des Penetriermittels so ausgewählt ist, dass sie zwischen 0.1 mg cm^{-2} und 15 mg cm^{-2}, bevorzugt zwischen 0.5 mg cm^{-2} und 10 mg cm^{-2}, besonders bevorzugt zwischen 0.75 mg cm^{-2} und 5 mg cm^{-2} und am meisten bevorzugt zwischen 1 mg cm^{-2} und 2.5 mg cm^{-2} beträgt, falls das genannte Corticosteroid eine therapeutische Wirkung in den tiefen subkutanen, z. B. Muskel- oder Gelenksgewebe oder sonstigen entfernten Geweben umfassend den gesamten Körper ausüben soll.

47. Verwendung der Formulierungen gemäß einem der vorangegangenen Ansprüche zur Herstellung eines Medikaments für die nichtinvasive Anwendung von Corticosteroiden,
dadurch gekennzeichnet, dass die Flächendosis ausgedrückt durch die pro Flächeneinheit aufgetragene Gesamttrockenmasse der Penetriermittel, zwischen 1 μg cm^{-2} und 250 μg cm^{-2}, bevorzugt zwischen 2.5 μg cm^{-2} und 100 μg cm^{-2}, mehr bevorzugt zwischen 5 μg cm^{-2} und 50 μg cm^{-2} und am meisten bevorzugt zwischen 7.5 μg cm^{-2} und 20 μg cm^{-2} beträgt, falls das genannte Corticosteroid eine hauptsächlich lokale, d. h. eher oberflächliche als systemische therapeutische Wirkung ausüben soll.

48. Verwendung der Formulierungen gemäß einem der vorangegangenen Ansprüche zur Herstellung eines Medikaments für die nichtinvasive Anwendung von Corticosteroiden, die mit den genannten Penetriermitteln in den Formulierungen assoziiert oder darin eingekapselt sind,
dadurch gekennzeichnet, dass die Formulierung durch Aufsprühen, Aufschmieren, Aufrollen oder Aufwischen auf die Anwendungsfläche, je nach Eignung insbesondere unter Verwendung eines Sprays, Spenders, einer Rolle oder Schwammes aufgetragen wird.

49. Verwendung einer Formulierung gemäß einem der vorangegangenen Ansprüche zur Herstellung eines Medikaments zur Behandlung von Entzündungskrankheiten, Dermatosen, Nieren- oder Leberversagen, Nebenniereninsuffizienz, Aspirationssyndrom, Behcet Syndrom, Bissen und Stichen, Blutkrankheiten wie die Grippe-Haemagglutinin-Krankheit, haemolytische Anämie, Hypereosinophilie, hypoplastische Anämie, Makroglobulinaemie, thrombocytopenische Purpura, weiterhin zur Behandlung von Knochenkrankheiten, Himödemen, Cogan's Syndrom, kongenitale Nebennierenhyperplasie, Bindegewebskrankheiten wie Flechte, Lupus erythematosus, Polymyalgia rheumatica, Polymyositis und Dermatomyositis, Epilepsie, Augenkrankheiten wie grauer Star, Graves' Ophthalmopathie, Haemangiome, Herpesinfektionen, Neuropathien, retinale Vasculitis, für einige gastrointestinale Krankheiten wie die "Inflammatory Bowel Disease", Übelkeit und Speiseröhrenschäden, für Hypercalcaemie, Infektionen, z. B. des Auges (wie bei entzündlicher Mononukleose), für die Kawasaki Krankheit, Myastenia Gravis, verschiedene Schmerzsyndrome wie postherpetische Neuralgien, für Polyneuropathien, Pancreatitis, bei Atemwegskrankheiten wie Asthma, zur Behandlung von rheumatischen Erkrankungen und Osteoarthritis, Rhinitis, Sarcoidosis, Hautkrankheiten wie Alopecia, Ekzemen, Erythema Multiforme, Flechte, Pemphigus und Pemphigoid, Psoriasis, Pyoderma Gangrenosum, Urticaria, im Falle von Thyroid- und Gefäßkrankheiten.

Revendications

1. Formulation comportant des éléments pénétrants qui sont capables de pénétrer dans les pores d'une barrière, même lorsque le diamètre moyen desdits pores est inférieur au diamètre moyen desdits éléments pénétrants, pourvu que les éléments pénétrants puissent transporter des agents, ou sinon permettent une perméation d'agents, à travers les pores après que les éléments pénétrants soient entrés dans les pores, les agents associés auxdits éléments pénétrants étant des corticostéroïdes, en particulier glucocorticoïdes ou minéralocorticostéroïdes, **caractérisée en ce que** la teneur relative en corticostéroïdes est supérieure à 0,1 % en poids par rapport à la masse sèche totale de la formulation, et
   la formulation comporte au moins un antioxydant selon une quantité qui réduit l'augmentation d'indice d'oxydation à moins de 100 % pour 6 mois.

2. Formulation selon la revendication 1,
   caractérisée en ce que la formulation comporte au moins un adjuvant de consistance selon une quantité qui augmente la viscosité de formulation au-dessus de celle de la formulation correspondante non-épaissie à une valeur maximale de 5 Ns/m^2 de sorte que l'étalement sur la zone d'application, et la rétention au niveau de celle-ci sont permis et/ou au moins un microbiocide selon une quantité qui réduit la numération bactérienne de 1 million de germes ajoutés par g de masse totale de la formulation à moins de 100 dans le cas de bactéries aérobies, à moins de 10 dans le cas d'entéro-bactéries, et à moins de 1 dans le cas de Pseudomonas aeruginosa ou Staphilococcus aureus, après une période de 4 jours.

3. Formulation selon la revendication 2,
   caractérisée en ce qu'au moins un adjuvant de consistance est ajouté selon une quantité qui augmente la viscosité de formulation jusqu'à 1 Ns/m^2 et de manière plus préférée jusqu'à 0,2 Ns/m^2.

4. Formulation selon les revendications 1 à 3,
   caractérisée en ce qu'au moins un antioxydant est ajouté selon une quantité qui réduit l'augmentation d'indice d'oxydation à moins de 100 % pour 12 mois et de manière plus préférée à moins de 50 % pour 12 mois.

5. Formulation selon les revendications 2 à 4,
   caractérisée en ce que ledit au moins un microbiocide est ajouté selon une quantité qui réduit la numération bactérienne de 1 million de germes aj outés par g de masse totale de la formulation à moins de 100 dans le cas de bactéries aérobies, à moins de 10 dans le cas d'entéro-bactéries, et à moins de 1 dans le cas de Pseudomonas aeruginosa ou Staphilococcus aureus, après une période de 3 jours, et de manière plus préférée après une période de 1 jour.

6. Formulation selon l'une quelconque des revendications 2 à 5,
   caractérisée en ce que l'adjuvant de consistance est sélectionné parmi des polymères hydrophiles pharmaceutiquement acceptables, tels que des dérivés de cellulose partiellement éthérifiés, comportant une carboxyméthyl-, hydroxyéthyl-, hydroxypropyl-, hydroxypropylméthyl- or méthyl-cellulose; des polymères hydrophiles complètement synthétiques comportant des polyacrylates, polyméthacrylates, poly(hydroxy-éthyl)-, poly(hydroxypropyl)-, poly(hydroxypropylméthyl)méthacrylate, polyacrylonitrile, méthallyl-sulfonate, polyéthylènes, polyoxyéthylènes, polyéthylèneglycols, polyéthylèneglycol-lactide, polyéthylèneglycol-diacrylate, polyvinylpyrrolidone, alcools polyvinyliques, poly(propylméthacrylamide), poly(propylène fumarate-co-éthylèneglycol), poloxamères, polyaspartamide, acide hyaluronique (réticulé par hydrazine), silicone ; des gommes naturelles comportant des alginates, carragénine, gomme de guar, gélatine, adragante, pectine (amidée), xanthane, collagène chitosane, agarose ; des mélanges et d'autres dérivés ou copolymères de ceux-ci et/ou autres polymères pharmaceutiquement acceptables, ou au moins biologiquement acceptables.

7. Formulation selon la revendication 6,
   caractérisée en ce que les fractions en poids de polymère sont dans la plage comprise entre 0,05 % et 10 %, de manière plus préférée sont dans la plage comprise entre 0,1 % et 5 %, de manière encore plus préférée sont dans la plage comprise entre 0,25 % et 3,5 % et de manière la plus préférée se trouvent dans la plage comprise entre 0,5 % et 2 %.

8. Formulation selon l'une quelconque des revendications 1 à 7,
   caractérisée en ce que l'antioxydant est sélectionné parmi des antioxydants phénoliques synthétiques, tels que l'hydroxyanisol butylé (BHA), hydroxytoluène butylé (BHT) et di-tert-butylphénol (LY178002, LY256548, HWA-

131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), butylhydroquinone tertiaire (TBHQ), gallate de propyle (PG), 1-O-hexyl-2,3,5-triméthyl-hydroquinone (HTHQ) ; des amines aromatiques, incluant diphénylamine, p-alkylthio-o-anisidine, dérivés d'éthylènediamine, carbazole et tétrahydroindénoindole ; des phénols et des acides phénoliques, incluant guaiacol, hydroquinone, vanilline, acides galliques et leurs esters, acide protocatéchuique, acide quinique, acide syringique, acide ellagique, acide salicylique, acide nordihydroguaiarétique (NDGA) et eugénol ; des tocophérols et leurs dérivés, incluant tocophéryl-acylate, -laurate, -myristate, - palmitate, -oléate, -linoléate, or tout autre tocophéryl-lipoate adapté, tocophéryl-POE-succinate; trolox et des analogues d'amide et de thiocarboxamide correspondants ; acide ascorbique et ses sels, isoascorbate, acides (2 or 3 or 6)-o-alkylascorbiques, esters ascorbyliques, incluant 6-o-lauroyle, myristoyle, palmitoyl-, oléoyl-, or linoléoyl-L-acide ascorbique; des agents anti-inflammatoires non-stéroïdiens (NSAIDs), tels que indométhacine, diclofénac, acide méfénamique, acide flufénamique, phénylbutazone, acide oxyphenbutazone acétylsalicylique, naproxène, diflunisal, ibuprofène, cétoprofène, piroxicam, pénicillamine, disulfure de pénicillamine, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phénobarbital, acétaminephène ; des acides aminosalicyliques et des dérivés ; méthotrexate, probucol, anti-arythmiques, incluant amiodarone, aprindine et asocaïnol ; ambroxol, tamoxifène, b-hydroxytamoxifène ; des antagonistes de calcium, incluant nifédipine, nisoldipine, nimodipine, nicardipine et nilvadipine, des bloqueurs de récepteur bêta incluant aténolol, propranolol et nébivolol ; bisulfite de sodium, métabisulfite de sodium, thiourée ; des agents chélatants, tels que EDTA, GDTA, desferral ; des systèmes de défense endogènes variés, tels que transferrine, lactoferrine, ferritine, céaruloplasmine, haptoglobion, haemopéxine, albumine, glucose, ubiquinol-10 ; des antioxydants enzymatiques, tels que superoxyde dismutase et des complexes métalliques ayant une activité similaire, incluant catalase, peroxydase de glutathione, et des molécules moins complexes, telles que bêta-carotène, bilirubine, acide urique ; des flavonoïdes incluant flavones, flavonols, flavonones, flavanonales et chacones, anthocyanines ; N-acétylcystéine, mesna, glutathione, des dérivés de thiohistidine, triazoles ; tannines, acide cinnamique, acides hydroxycinnamatiques et leurs esters, incluant des acides coumariques et esters d'acide caféique et leurs esters, acide férulique, acide (iso-)chlorogénique et acide sinapique ; des extraits d'épice incluant des extraits d'épice provenant de clous de girofle, de cannelle, de sauge, de romarin, de macis, d'origan, de piment de la jamaïque, et de noix de muscade ; acide carnosique, carnosol, acide carsolique ; acide rosmarinique, rosmaridiphénol, acide gentisique, acide férulique ; des extraits de farine d'avoine, tels qu'avénanthramide 1 et 2; des thioéthers, dithioéthers, sulfoxydes, disulfides de tétralkylthiurame ; acide phytique, dérivés stéroïdes, incluant U74006F ; des métabolites de tryptophane, incluant 3-hydroxykynurénine et acide 3-hydroxyanthranilique ; et des organochalcogénides.

9. Formulation selon la revendication 8,

caractérisée en ce que la concentration de BHA ou BHT est comprise entre 0,001 et 2 % en poids, de manière plus préférée est comprise entre 0,0025 et 0,2 % en poids, et de manière la plus préférée est comprise entre 0,005 et 0,02 % en poids, la concentration de TBHQ et PG est comprise entre 0,001 et 2 % en poids, de manière plus préférée est comprise entre 0,005 et 0,2 % en poids, et de manière la plus préférée est comprise entre 0,01 et 0,02 % en poids, la concentration de tocophérols est comprise entre 0,005 et 5 % en poids, de manière plus préférée est comprise entre 0,01 et 0,5 % en poids, et de manière la plus préférée est comprise entre 0,05 et 0,075 % en poids, la concentration d'esters d'acide ascorbique est comprise entre 0,001 et 5, de manière plus préférée est comprise entre 0,005 et 0,5, et de manière la plus préférée est comprise entre 0,01 et 0,15 % en poids, la concentration d'acide ascorbique est comprise entre 0,001 et 5, de manière plus préférée est comprise entre 0,005 et 0,5 % en poids, et de manière la plus préférée est comprise entre 0,01 et 0,1 % en poids, la concentration de bisulfite de sodium ou de métabisulfite de sodium est comprise entre 0,001 et 5, de manière plus préférée est comprise entre 0,005 et 0,5 % en poids, et de manière la plus préférée est comprise entre 0,01 et 0,15 % en poids, la concentration de thiourée est comprise entre 0,0001 et 2 % en poids, de manière plus préférée est comprise entre 0,0005 et 0,2, et de manière la plus préférée est comprise entre 0,001 et 0,01 % en poids, de manière la plus typique est de 0,005 % en poids, la concentration de cystéine est comprise entre 0,01 et 5, de manière plus préférée est comprise entre 0,05 et 2 % en poids, et de manière la plus préférée est comprise entre 0,1 et 1,0 % en poids, et de manière la plus typique est de 0,5 % en poids, la concentration de monothioglycérol est comprise entre 0,01 et 5 % en poids, de manière plus préférée est comprise entre 0,05 et 2 % en poids, et de manière la plus préférée est comprise entre 0,1 et 1,0 % en poids, et de manière la plus typique est de 0,5 % en poids, la concentration de NDGA est comprise entre 0,0005 et 2 % en poids, de manière plus préférée est comprise entre 0,001 et 0,2 % en poids, et de manière la plus préférée est comprise entre 0,005 et 0,02 % en poids, de manière la plus typique est de 0,01 % en poids, la concentration de glutathione est comprise entre 0,005 et 5 % en poids, de manière plus préférée est comprise entre 0,01 et 0,5 % en poids, et de manière la plus préférée est comprise entre 0,05 et 0,2 % en poids, de manière la plus typique est de 0,1 % en poids, la concentration de EDTA est comprise entre 0,001 et 5 % en poids, de manière encore plus préférée est comprise entre 0,005 et 0,5 % en poids, et de manière la plus préférée est comprise entre 0,01 et 0,2 % en poids, de manière la plus typique entre

0,05 et 0,975 % en poids, la concentration d'acide citrique est comprise entre 0,001 et 5 % en poids, de manière encore plus préférée est comprise entre 0,005 et 3 % en poids, et de manière la plus préférée est comprise entre 0,01 et 0,2, de manière la plus typique entre 0,3 et 2 % en poids.

10. Formulation selon l'une quelconque des revendications 2 à 9,
caractérisée en ce que le microbiocide est sélectionné parmi des alcools à chaîne courte, comportant l'alcool éthylique et isopropylique, chlorbutanol, alcool benzylique, alcool chlorbenzylique, alcool dichlorbenzylique, hexachlorophène; des composés phénoliques, tels que crésol, 4-chloro-m-crésol, p-chloro-m-xylénol, dichlorophène, hexachlorophène, povidon-iode ; des parabènes, en particulier des alkyl-parabènes, tels que méthyl-, éthyl-, propyl-, ou butyl-parabène, benzyl-parabène ; des acides, tels que l'acide sorbique, l'acide benzoïque et leurs sels ; des composés d'ammonium quaternaires, tels que des sels d'alkonium, par exemple un bromure, des sels de benzalkonium, tels qu'un chlorure ou un bromure, des sels de cétrimonium, par exemple un bromure, des sels de phénoalkécinium, tels que du bromure de phénododécinium, chlorure de cétylpyridinium et autres sels ; des composés de mercure, tels que l'acétate, du borate, ou nitrate phénylmercurique, thiomersal, chlorhexidine or son gluconate, ou tout composé antibiotiquement actif d'origine biologique, ou tout mélange de ceux-ci.

11. Formulation selon la revendication 10,
caractérisée en ce que la concentration nominale d'alcools à chaîne courte dans le cas de l'alcool éthylique, propylique, butylique ou benzylique va jusqu'à 10 % en poids, de manière plus préférée va jusqu'à 5 % en poids, et de manière la plus préférée se trouve dans la plage comprise entre 0,5 et 3 % en poids, dans le cas du chlorobutanol se trouve dans la plage comprise entre 0,3 et 0,6 % en poids ; la concentration nominale de parabènes, en particulier dans le cas de méthyl-parabène, se trouve dans la plage comprise entre 0,05 et 0,2 % en poids, et dans le cas de propyl-parabène se trouve dans la plage comprise entre 0,002 et 0,02 % en poids ; la concentration nominale d'acide sorbique se trouve dans la plage comprise entre 0,05 et 0,2 % en poids, et dans le cas de l'acide benzoïque se trouve dans la plage comprise entre 0,1 et 0,5 % en poids ; la concentration nominale de phénols, triclosan, se trouve dans la plage comprise entre 0,1 et 0,3 % en poids, et la concentration nominale de chlorhexidine se trouve dans la plage comprise entre 0,01 et 0,05 % en poids.

12. Formulation selon l'une quelconque des revendications précédentes,
caractérisée en ce que le corticostéroïde est sélectionné parmi le dipropionate d'alclonétasone, amcinonide, dipropionate de béclométhasone, bêtaméthasone, 17-valérate de bêtaméthasone, 17,21-divalérate de bêtaméthasone, 21-acétate de bêtaméthasone, 21-butyrate de bêtaméthasone, 21-propionate de bêtaméthasone, 21-valérate de bêtaméthasone, benzoate de bêtaméthasone, dipropionate de bêtaméthasone, valérate de bêtaméthasone, budesonide, propionate de clobétasol, butyrate de clobétasone, cortexolone, corticostérone, cortisone, 17-acétate de cortisone, 21-désoxybêtaméthasone, 17-propionate de 21-désoxybêtaméthasone, désoxycorticostérone, désonide, désoxyméthasone, dexaméthasone, diacétate de diflorasone, valérate de diflucortolone, acétonide de fluclorolone, pivalate de fluméthasone, acétonide de fluocinolone, fluocinonide, butyle de fluocortine, fluocortolone, 9-alpha-fluorocortisone, 9-alpha-fluorohydrocortisone, 9-alpha-fluoroprednisolone, acétate de fluprednidène, flurandrénolone, halcinonide, hydrocortisone, 17-acétate d'hydrocortisone, 17-butyrate d'hydrocortisone, 17-propionate d'hydrocortisone, 17-valérate d'hydrocortisone, 21-acétate d'hydrocortisone, 21-butyrate d'hydrocortisone, 21-propionate d'hydrocortisone, 21-valérate d'hydrocortisone, 17-alpha-hydroxyprogestérone, acétate de méthylprednisolone, furoate de mométasone, prednisolone, prednisone, 17-acétate de prednisone, 17-valérate de prednisone, progestérone, triamcinolone, acétonide de triamcinolone.

13. Formulation selon l'une quelconque des revendications précédentes,
caractérisée en ce que les éléments pénétrants sont mis en suspension ou dispersés dans un liquide polaire sous la forme de gouttelettes de fluide entourées d'un revêtement de type membrane constitué d'une ou plusieurs couches, ledit revêtement comportant au moins deux types ou formes de substances amphiphiles ayant une tendance à s'agréger, pourvu que lesdites au moins deux substances diffèrent d'au moins un facteur de 10 en termes de solubilité dans ledit liquide ou sinon que lesdites substances, lorsque sous la forme d'homo-agrégats, pour la substance plus soluble, ou d'hétéro-agrégats, pour toute combinaison desdites deux substances, ont un diamètre moyen préféré plus petit que le diamètre des homo-agrégats contenant purement la substance moins soluble, ou pourvu sinon que la présence de la substance plus soluble abaisse l'énergie élastique moyenne du revêtement de type membrane à proximité de l'énergie thermique.

14. Formulation selon la revendication 13,
caractérisée en ce que la substance plus soluble a tendance à solubiliser la gouttelette et le contenu de cette substance s'élève jusqu'à 99 % en mole de la concentration de solubilisation ou correspond sinon jusqu'à

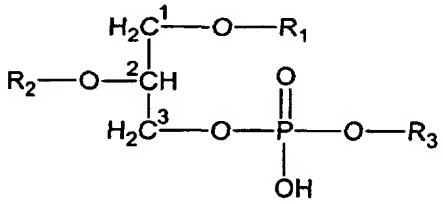
99 % en mole de la concentration de saturation dans la gouttelette non-solubilisée, ce qui est supérieur.

15. Formulation selon la revendication 14,
caractérisée en ce que le contenu de la substance plus soluble est inférieur à 50 %, en particulier inférieur à 40 % et de manière la plus préférée inférieur à 30 %, de ladite concentration de solubilisation de ladite substance.

16. Formulation selon la revendication 14,
caractérisée en ce que le contenu de la substance plus soluble est inférieur à 80 %, de préférence inférieur à 65 % et de manière la plus préférée inférieur à 50 %, de ladite concentration de saturation de ladite substance dans la gouttelette.

17. Formulation selon l'une quelconque des revendications 13 à 16,
caractérisée en ce que la substance moins soluble parmi les substances s'agrégeant est un lipide ou un matériel de type lipide, en particulier un lipide polaire, alors que la substance qui est plus soluble dans le liquide en suspension et qui augmente la capacité d'adaptation de la gouttelette appartient à la famille des tensioactifs ou présente sinon des propriétés de type tensioactif.

18. Formulation selon la revendication 17,
caractérisée en ce que le lipide ou matériel de type lipide est un lipide ou un lipoïde provenant d'une source biologique ou un lipide synthétique correspondant ou l'une quelconque de ses modifications, ledit lipide appartenant de préférence à la classe de phospholipides purs ayant la formule chimique suivante :



où R_1 et R_2 sont une chaîne aliphatique, typique C_{10-20}-acyle, ou -alkyle ou un résidu d'acide gras partiellement insaturé, en particulier une chaîne oléoyl-, palmitoéloyl-, élaïdoyl-, linoléyl-, linolényl-, linolénoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or stéaroyl; et où R_3 est l'hydrogène, 2-triméthylamino-1-éthyle, 2-amino-1-éthyle, C_{1-4}-alkyle, C_{1-5}-alkyle substitué par carboxy, C_{2-5}-alkyle substitué par hydroxy, C_{2-5}-alkyle substitué par carboxy et hydroxy, ou C_{2-5}-alkyle substitué par carboxy et groupe amino, inositol, sphingosine, ou des sels desdites substances, ledit lipide comportant également des glycérides, lipides isoprénoïdes, stéroïdes, stérines ou stérols, des lipides contenant du soufre ou hydrate de carbone, ou tout autre lipide de formation de bicouche, en particulier des acides gras de fluide semi-protonés, ledit lipide est sélectionné parmi le groupe comportant des phosphatidylcholines, phosphatidyléthanolamines, phosphatidylglycérols, phosphatidylinositols, acides phosphatidiques, phosphatidylsérines, sphingomyélines ou autres sphingophospholipides, glycosphingolipides (incluant cérébrosides, céramide-polyhexosides, sulfatides, sphingoplasmalogènes), gangliosides et autres glycolipides or lipides synthétiques, en particulier avec des dérivés de sphingosine correspondants, ou tout autre glycolipide, de sorte que deux chaînes similaires ou différentes peuvent être liées par groupes esters à l'ossature (comme dans un composé diacyle et dialénoyle) ou être attachées à l'ossature à l'aide de liaisons éther, comme dans des lipides dialkyliques.

19. Formulation selon la revendication 17,
caractérisée en ce que le tensioactif ou matériel de type tensioactif est un tensioactif non-ionique, zwitterion, anionique or cationique, en particulier un acide gras ou un alcool gras, un sel d'alkyl-tri/di/méthylammonium, un sel d'alkylsulfate, a sel monovalent de cholate, désoxycholate, glycocholate, glycodésoxycholate, taurodésoxycholate, taurocholate, un acyl- ou alkanoyl-diméthyl-aminoxyde, en particulier un dodécyl-diméthyl-aminoxyde, un alkyl- or alkanoyl-N-méthylglucamide, N-alkyl-N,N-diméthylglycine, 3-(acyldiméthylammonio)-alkanesulfonate, N-acyl-sulfobétaïne, un éther de polyéthylèneglycol-octylphényle, en particulier un éther de nonaéthylèneglycol-octylphényle, un éther de polyéthylène-acyle, en particulier un éther de nonaéthylène-dodécyle, un éther de polyéthylèneglycol-isoacyle, en particulier un éther d'octaéthylèneglycol-isotridécyle, un éther de polyéthylène-acyle, en particulier un éther d'octaéthylènedodécyle, un ester de polyéthylèneglycol-sorbitane-acyle, tel que polyéthylèneglycol-20-monolaurate (Tween 20) ou polyéthylèneglycol-20-sorbitan-monooléate (Tween 80), un éther de

polyhydroxyéthylène-acyle, en particulier un éther de polyhydroxyéthylène-lauryle, -myristoyl, -cétylstéaryle, ou -oléoyle, comme dans un éther de polyhydroxyéthylene-4 ou 6 ou 8 ou 10 ou 12, etc., -lauryle (comme dans la série Brij), or dans l'ester correspondant, par exemple d'un type polyhydroxyéthylène-8-stéarate (Myrj 45), -laurate or -oléate, ou dans une huile de castor polyéthoxylée 40, sorbitane-monoalkylate (par exemple dans Arlacel ou Span), en particulier sorbitane-monolaurate, un acyl- ou alkanoyl-N-méthylglucamide, en particulier dans décanoyl- ou dodécanoyl-N-méthylglucamide, un alkyl-sulfate (sel), par exemple dans un lauryl- ou oleoyl-sulfate, désoxycholate de sodium, glycodésoxycholate de sodium, oléate de sodium, taurate de sodium, un sel d'acide gras, tel qu'élaïdate de sodium, linoléate de sodium, laurate de sodium, un lysophospholipide, tel que acide n-octadécylène(= oléoyl)-glycérophosphatidique, -phosphorylglycérol, ou -phosphorylsérine, n-acyl-, par exemple acide lauryl- ou oléoyl-glycéro-phosphatidique, -phosphorylglycérol, or -phosphorylsérine, acide n-tétradécyl-glycéro-phosphatidique, -phosphorylglycérol, ou -phosphorylsérine, un palmitoéloyl-, élaidoyl-, vaccényl-lysophospholipide correspondant ou un phospholipide à chaîne courte correspondant, ou sinon un polypeptide tensioactif.

20. Formulation selon l'une quelconque des revendications 13 à 19,
caractérisée en ce que le diamètre de l'élément pénétrant moyen est compris entre 30 nm et 500 nm, de préférence entre 40 nm et 250 nm, de manière encore plus préférée entre 50 nm et 200 nm et de manière la plus préférée entre 60 nm et 150 nm.

21. Formulation selon l'une quelconque des revendications 13 à 19,
caractérisée en ce que le diamètre moyen de l'élément pénétrant est 2 à 25 fois plus grand que le diamètre moyen des pores de la barrière, de préférence entre 2,25 et 15 fois plus grand, de manière encore plus préférée entre 2,5 et 8 fois plus grand et de manière la plus préférée entre 3 et 6 fois plus grand que ledit diamètre de pore moyen.

22. Formulation selon l'une quelconque des revendications 13 à 21,
caractérisée en ce que le poids sec de toutes les gouttelettes de support dans une formulation destinée à être utilisée sur la peau d'un être humain ou d'un animal est de 0,01 % en poids (% en p) à 40 % en poids de la masse de formulation totale, en particulier entre 0,1 % en poids et 30 % en poids, de manière particulièrement préférée entre 0,5 % en poids et 20 % en poids, et de manière la plus préférée entre 1 % en poids et 10 % en poids.

23. Formulation selon l'une quelconque des revendications 13 à 21,
caractérisée en ce que le poids sec de toutes les gouttelettes de support dans une formulation destinée à être utilisée sur une muqueuse d'un être humain ou d'un animal est de 0,0001 % en poids à 30 % en poids de la masse de formulation totale.

24. Formulation selon l'une quelconque des revendications 1 à 23,
caractérisée en ce que le pH de la suspension de support est compris entre 4 et 10, de préférence entre 5 et 9, et de manière plus préférée souvent jusqu'à 8,5, comme nécessaire pour maximaliser la stabilité de formulation.

25. Procédé pour préparer une formulation pour une application non-invasive in vivo, selon l'une quelconque des revendications précédentes,
caractérisé en ce que des éléments pénétrants capables de s'associer et/ou d'incorporer lesdites molécules d'agent sont formés à partir d'au moins une substance amphiphile, au moins un fluide polaire, au moins une substance active en termes de bord ou tensioactif, au moins un corticostéroïde selon une quantité de plus de 0,1 % en poids sur la base de la masse sèche totale de la formulation, et, dans ce cas, d'autres ingrédients classiques, qui forment ensemble ladite formulation.

26. Procédé selon la revendication 25,
caractérisé en ce qu'au moins une substance active en termes de bord ou tensioactif, au moins une substance amphiphile, au moins un fluide hydrophile et l'agent sont dissous pour former une solution et, si nécessaire, sont mélangés séparément, les mélanges (partiels) ou solutions résultants étant alors combinés pour induire par la suite, de préférence par action d'une énergie mécanique, tel qu'en agitant, en remuant, par vibration, homogénéisation, traitement aux ultrasons, cisaillement, congélation et décongélation, ou filtration en utilisant une pression d'entraînement commode, la formation d'éléments pénétrants qui s'associent à l'agent et/ou s'incorporent dans celui-ci.

27. Procédé selon les revendications 25 ou 26,

caractérisé en ce que lesdites substances amphiphiles sont utilisées telles quelles, ou dissoutes dans un fluide polaire physiologiquement compatible, qui peut être de l'eau ou être miscible à l'eau, ou dans un agent de régulation de solvation, ensemble avec une solution polaire.

28. Procédé selon les revendications 25 ou 26,
caractérisé en ce que lesdites substances amphiphiles sont dissoutes dans des alcools très volatils, en particulier de l'éthanol, ou dans des solvants organiques pharmaceutiquement acceptables, qui sont alors retirés, par exemple par évaporation, avant de réaliser la préparation finale.

29. Procédé selon les revendications 27 ou 28,
caractérisé en ce que la solution polaire contient au moins substance active en termes de bord ou tensioactif.

30. Procédé selon l'une quelconque des revendications 25 à 29,
caractérisé en ce que la formation desdits éléments pénétrants est induite par l'ajout de substances nécessaires dans une phase de fluide, par évaporation à partir d'une phase inverse, par injection ou dialyse, si nécessaire sous l'influence d'une contrainte mécanique, tel qu'en agitant, en remuant, en particulier en remuant à vitesse élevée, par vibration, homogénéisation, traitement aux ultrasons, cisaillement, congélation et décongélation, ou filtration en utilisant une pression d'entraînement commode, en particulier faible (1 MPa) ou intermédiaire (jusqu'à 10 MPa).

31. Procédé selon la revendication 30,
caractérisé en ce que la formation desdits éléments pénétrants est induite par filtration, le matériau filtrant ayant des tailles de pores comprises entre 0,01 μm et 0,8 μm, de préférence entre 0,02 μm et 0,3 μm, et de manière la plus préférée entre 0,05 μm et 0,15 μm, de sorte que plusieurs filtres peuvent être utilisés séquentiellement ou en parallèle.

32. Procédé selon l'une quelconque des revendications 25 à 31,
caractérisé en ce que lesdits agents et éléments pénétrants sont amenés à s'associer, au moins partiellement, après la formation desdits éléments pénétrants, par exemple après injection d'une solution du médicament dans un fluide pharmaceutiquement acceptable, tel que de l'éthanol, 1- et 2-propanol, alcool benzylique, propylèneglycol, polyéthylèneglycol (poids moléculaire : 200 à 400 D) ou glycérol dans le milieu en suspension, lesdits éléments pénétrants étant formés au préalable, en utilisant le procédé de fabrication correspondant ou un certain autre adapté, ou simultanément à l'injection de médicament, si on a besoin d'utiliser une co-solution du de médicament, si on a besoin d'utiliser une co-solution du médicament et, au moins certains ingrédients pénétrants.

33. Procédé selon l'une quelconque des revendications 25 à 32,
caractérisé en ce que lesdits éléments pénétrants, avec lesquels les molécules d'agent sont associées et/ou dans lesquels l'agent est incorporé, sont préparés juste avant l'application de la formulation, si commode, à partir d'un concentré adapté ou d'un lyophilisat.

34. Procédé selon l'une quelconque des revendications 1 à 24,
caractérisé en ce que la teneur en corticostéroïdes est comprise entre 0,1 % en poids et 20 % en poids, de manière plus préférée entre 0,25 % en poids et 10 % en poids et de manière encore plus préférée entre 0,5 % en poids et 5 % en poids, par rapport à la masse sèche totale des supports chargés en médicament.

35. Formulation selon la revendication 34,
caractérisée en ce que la teneur relative en corticostéroïdes dans le cas du triamcinolone ou d'un de ses dérivés, tel que l'acétonide, est inférieure à 2 % en poids, par rapport à la masse sèche totale des supports chargés en médicament, de manière encore plus préférée est inférieure à 1 % en poids et de manière la plus préférée est inférieure à 0,5 % en poids.

36. Formulation selon la revendication 34,
caractérisée en ce que la teneur relative en corticostéroïdes dans le cas de l'hydrocortisone ou d'un de ses dérivés est inférieure à 20 % en poids, par rapport à la masse sèche totale des supports chargés en médicament, de manière encore plus préférée est inférieure à 12,5 % en poids et de manière la. plus préférée est inférieure à 5 % en poids.

37. Formulation selon la revendication 34, .

caractérisée en ce que la teneur relative en corticostéroïdes dans le cas du dexaméthasone ou d'un de ses dérivés est inférieure à 15 % en poids, par rapport à la masse sèche totale des supports chargés en médicament, de manière encore plus préférée est inférieure à 10 % en poids et de manière la plus préférée est inférieure à 5 % en poids.

38. Formulation selon la revendication 34,

caractérisée en ce que la teneur relative en corticostéroïdes dans le cas du clobétasol ou d'un de ses dérivés, tels que le propionate, est inférieure à 15 % en poids, par rapport à la masse sèche totale des supports chargés en médicament, de manière encore plus préférée est inférieure à 10 % en poids et de manière la plus préférée est inférieure à 5 % en poids.

39. Formulation selon les revendications 34 à 38,

caractérisée en ce que la teneur en corticostéroïdes est inférieure au maximum de saturation, défini comme la teneur en corticostéroïde à laquelle le corticostéroïde commence à cristalliser à l'intérieur ou à l'extérieur du support.

40. Formulation selon les revendications 1 à 24 et 34 à 37,

caractérisée en ce qu'afin d'accélérer l'action du médicament, un activateur de perméation est ajouté.

41. Formulation selon la revendication 40,

caractérisée en ce que l'activateur de perméation est sélectionné parmi des 1-acyl-azacycloheptan-2-ones (azones), 1-acyl-glucosides, 1-acyl-polyoxyéthylènes, 1-acyl-saccharides, 2-n-acyl-cyclohexanones, 2-n-acyl-1,3-dioxolanes (SEPA), 1,2,3-triacyl-glycérols, 1-alkanols, acides 1-alkanoïques, 1-alkylacétates, 1-alkylamines, 1-alkyl-n-alkyl-polyoxyéthylènes, 1-alkyl-alkylates, n-alkyl-bêta-D-thioglucosides, 1-alkyl-glycérides, 1-alkyl-propylèneglycols, 1-alkyl-polyoxyéthylènes, (1-alkyl-)2-pyrrolidones, alkyl-acétoacétates, alkylèneglycols, alkyl-méthyl-sulfoxydes (alkyl-DMSO), alkyl-propionates, alkyl-sulfates, diacyl-succinates, diacyl-N,N-diméthylaminoacétates (DDAA), diacyl-N,N-diméthylaminoisopropionates (DDAIP), phényl-alkylamines.

42. Formulation selon la revendication 41,

caractérisée en ce que la plage de concentration nominale des activateurs utilisés va jusqu'à 5 % pour le 1-capryl-propylèneglycol, 6 à 10 % pour 1-[2-(décylthio)éthyl]azacyclopentane-2-one (=HPE-101), < 10 % pour 1-dodécanol, < 10 % pour 1-dodécyl-azacycloheptan-2-one (=azone), environ 10% pour 2-n-nonyl-1,3-dioxolane (SEPA), < 10 % pour 2-n-octylcyclohexanone, jusqu'à 20 % pour DMSO et entre 5 % et 40 % pour l'éthanol, au moins 10 % pour l'éthylèneglycol, jusqu'à 30 % pour l'acétate d'éthyle, 5-50 % pour le glycérol, jusqu'à 75 % pour l'isopropanol, 1-20 % pour le myristate d'isopropyle, entre 1 et 20 % pour l'acide oléique et l'alcool d'oléyle, environ 1 % pour l'oléyl-polyoxyéthylène-ether, au moins 10 % pour le propylèneglycol..

43. Formulation selon les revendications 1 à 24 et 34 à 42,

caractérisée en ce que ledit corticostéroïde est ajouté selon une quantité qui permet à la formulation d'être appliquée en correspondant à une dose surfacique, comme exprimé par la masse sèche totale de l'élément pénétrant appliqué par surface unitaire, comprise entre 0,1 mg cm^{-2} et 15 mg cm^{-2}, de manière plus préférée 0,5 mg cm^{-2} et 10 mg cm^{-2}, de manière particulièrement préférée entre 0,75 mg cm^{-2} et 5 mg cm^{-2} et de manière la plus préférée entre 1 mg cm^{-2} et 2,5 mg cm^{-2}, si on souhaite que ledit corticostéroïde exerce un effet thérapeutique dans le tissu sous—cutané profond, par exemple muscle ou articulations, ou sinon dans les tissus éloignés, incluant le corps entier.

44. Formulation selon les revendication 1 à 24 et 34 à 42,

caractérisée en ce que ledit corticostéroïde est ajouté selon une quantité qui permet à la formulation d'être appliquée à l'aide d'une dose surfacique, comme exprimé par la masse sèche totale d'élément pénétrant appliqué par surface unitaire, comprise entre 1 µg cm^{-2} et 250 µg cm^{-2}, de manière plus préférée entre 2,5 et 100 µg cm^{-2}, de manière encore plus préférée entre 5 µg cm^{-2} et 50 µg cm^{-2}, et de manière la plus préférée entre 7,5 µg cm^{-2} et 20 µg cm^{-2}, si on souhaite que ledit corticostéroïde exerce un effet thérapeutique principalement local, c'est-à-dire superficiel, plutôt que systémique.

45. Formulation selon les revendications 1 à 24 et 34 à 44,

caractérisée en ce que la consistance et, si nécessaire d'autres caractéristiques de la formulation, sont sélectionnées de manière appropriée pour permettre une pulvérisation, un frottement, un roulement ou un épon-

gement de la formulation sur la zone d'application en particulier en utilisant un dispositif de pulvérisation, un dispositif de distribution, un rouleau ou une éponge, comme approprié.

46. Utilisation des formulations selon l'une quelconque des revendications précédentes, pour la préparation d'un médicament destiné à l'application non-invasive de corticostéroïdes,

caractérisée en ce que la dose surfacique, comme exprimé par la masse sèche totale de l'élément pénétrant appliqué par surface unitaire, est sélectionnée pour être comprise entre 0,1 mg cm^{-2} et 15 mg cm^{-2}, de manière préférée entre 0,5 mg cm^{-2} et 10 mg cm^{-2}, de manière particulièrement préférée entre 0,75 mg cm^{-2} et 5 mg cm^{-2} et de manière la plus préférée entre 1 mg cm^{-2} et 2,5 mg cm^{-2}, si on souhaite que ledit corticostéroïde exerce un effet thérapeutique dans le tissu sous—cutané profond, par exemple muscle ou articulations, ou sinon dans les tissus éloignés, incluant le corps entier.

47. Utilisation des formulations selon l'une quelconque des revendications précédentes, pour la préparation d'un médicament destiné à l'application non-invasive de corticostéroïdes,

caractérisée en ce que la dose surfacique, comme exprimé par la masse sèche totale d'éléments pénétrants appliqués par surface unitaire, est comprise entre 1 µg cm^{-2} et 250 µg cm^{-2}, de préférence entre 2,5 µg cm^{-2} et 100 µg cm^{-2}, de manière plus préférée entre 5 µg cm^{-2} et 50 µg cm^{-2}, et de manière la plus préférée entre 7,5 µg cm^{-2} et 20 µg cm^{-2}, si on souhaite que ledit corticostéroïde exerce un effet thérapeutique principalement local, c'est-à-dire superficiel, plutôt que systémique.

48. Utilisation des formulations selon l'une quelconque des revendications précédentes, pour la préparation d'un médicament destiné à l'application non-invasive de corticostéroïdes associés auxdits éléments pénétrants des formulations, ou encapsulés dans ceux-ci,

caractérisée en ce que la formulation est appliquée par pulvérisation, frottement, roulement ou épongement sur la zone d'application en particulier en utilisant un dispositif de pulvérisation, un dispositif de distribution, un rouleau ou une éponge, comme approprié.

49. Utilisation d'une formulation selon l'une quelconque des revendications précédentes, pour la préparation d'un médicament destiné au traitement d'une maladie inflammatoire, dermatose, défaillance rénale ou hépatique, insuffisance surrénale, syndrome d'aspiration, syndrome de Behcet, morsures et piqûres, troubles sanguins, tels que la maladie des agglutinines froides, anémie hémolytique, hyperéosinophilie, anémie hypoplasique, macroglobulinémie, purpura thrombocytopénique, destiné de plus à la gestion de troubles osseux, d'oedème cérébral, de syndrome de Cogan, d'hyperplasie surrénale congénitale, troubles de tissu conjonctif, tels que lichen, lupus érythémateux, pseudopolyarthrite rhizomélique, polymyosite et dermatomyosite, épilepsie, troubles de l'oeil, tels que des cataractes, ophtalmopathie de Graves, hémangiomc, infections d'herpès, neuropathies, vasculite rétinale, sclérite, et de certains troubles gastro-intestinaux, tels qu'une maladie inflammatoire de l'intestin, des nausées et une lésion de l'oesophage, d'une hypercalcémie, infections, par exemple de l'oeil (telles que des infections mononucléoses), de la maladie de Kawasaki, myasthénie gravis, divers syndromes de douleur, tels qu'une neuralgie postherpétique, de polyneuropathies, pancréatite, pour des troubles respiratoires tels que l'asthme, pour la gestion d'une maladie rhumatoïde et l'ostéoarthrite, rhinite, sarcoïdose, maladies de la peau, telles que alopécie, eczéma, érythème multiforme, lichen, pemphigus et pemphigoïde, psoriasis, idiophagédénisme, urticaire, dans le cas de troubles de la thyroïde et vasculaires.

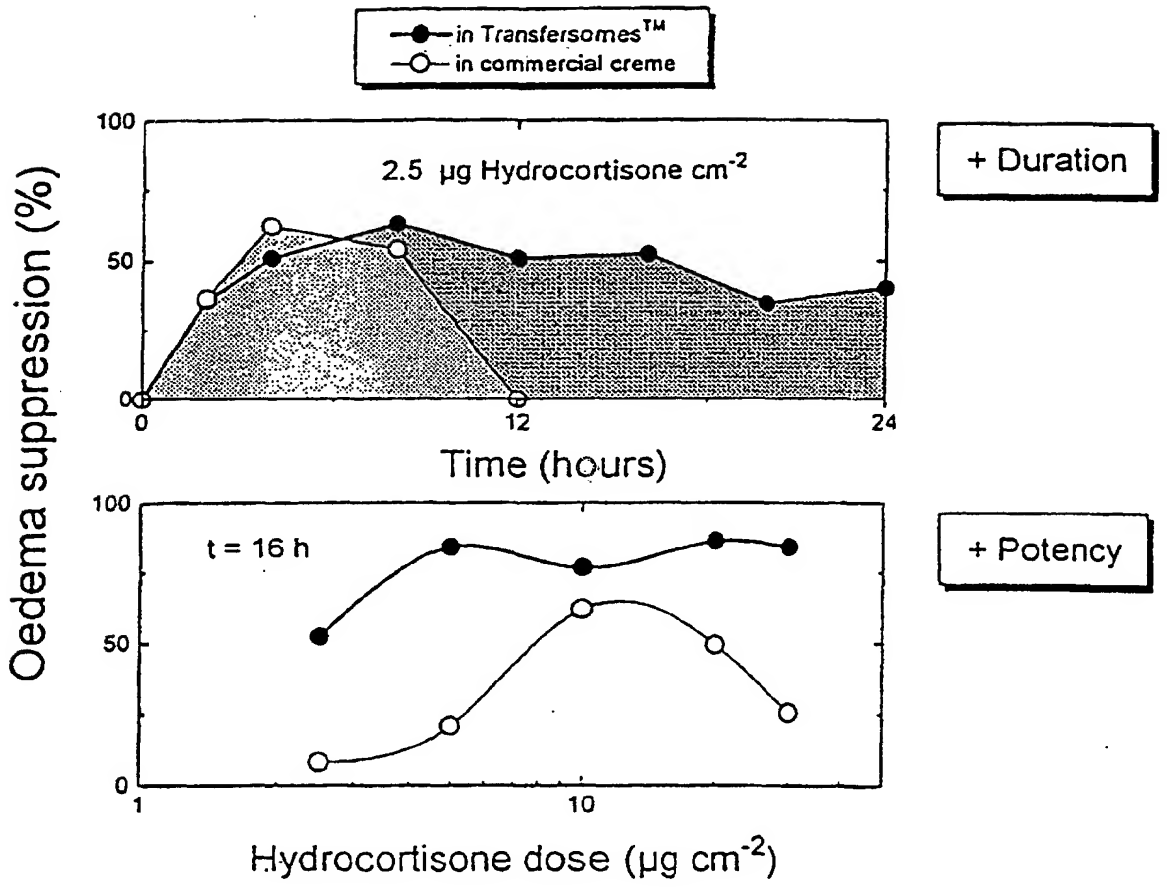

in Transfersomes™
in commercial creme
2.5 µg Hydrocortisone cm-2
+ Duration
Oedema suppression (%)
100
50
0
0
12
24
Time (hours)
t = 16 h
+ Potency
100
50
0
1
10
Hydrocortisone dose (µg cm-2)

Figure 1

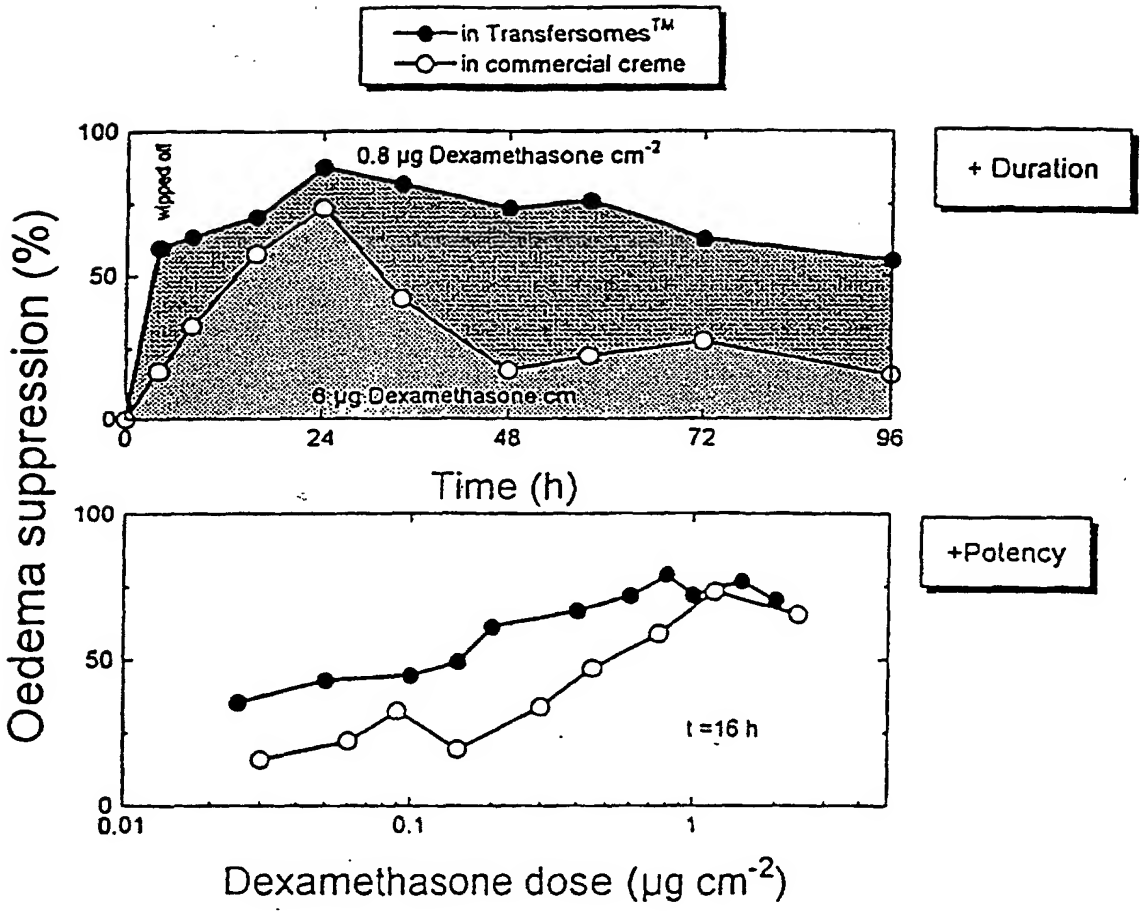

in Transfersomes™
in commercial creme
100
50
0
wipped off
0.8 µg Dexamethasone cm-2
6 µg Dexamethasone cm
0
24
48
72
96
Time (h)
+ Duration
Oedema suppression (%)
100
50
0
0.01
0.1
1
t =16 h
+Potency
Dexamethasone dose (µg cm-2)

Figure 2

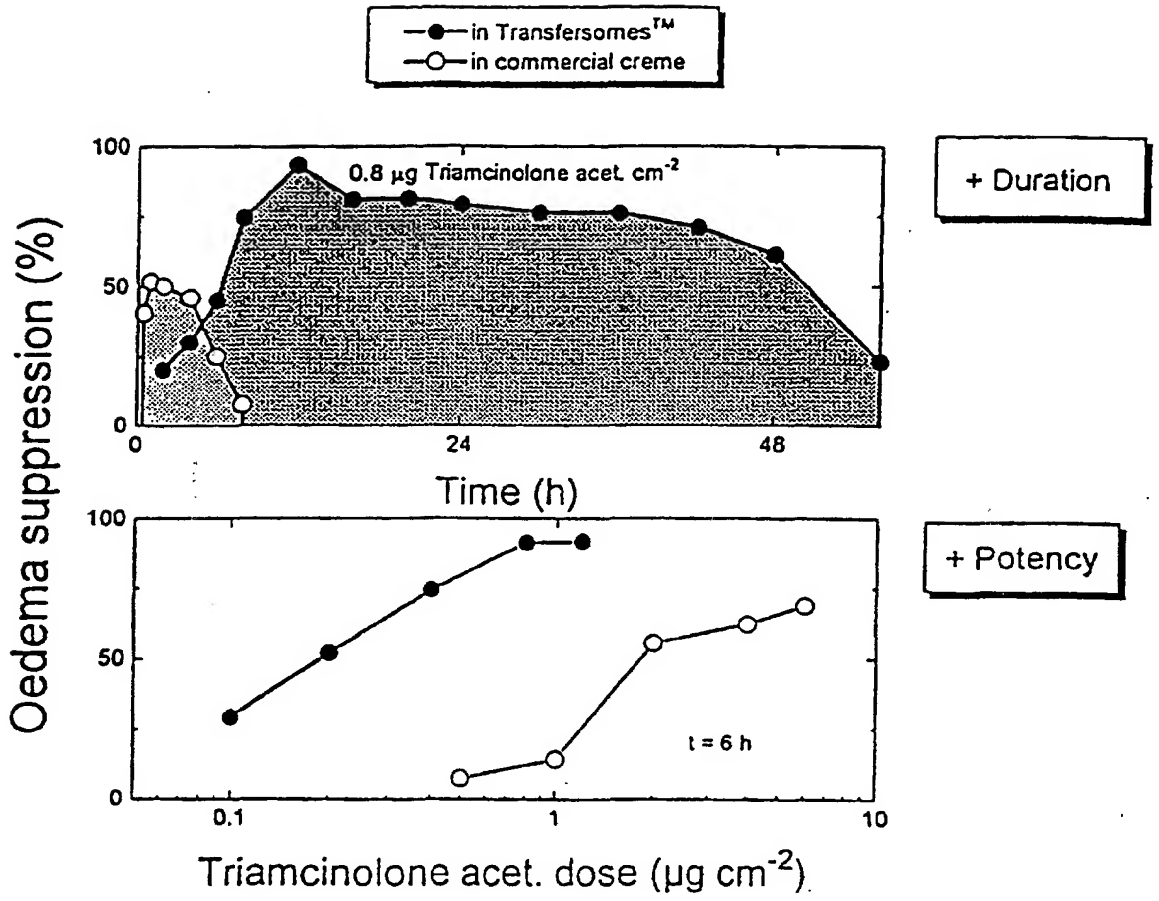

in Transfersomes™
in commercial creme
0.8 µg Triamcinolone acet. cm-2
+ Duration
Oedema suppression (%)
100
50
0
0
24
48
Time (h)
+ Potency
t = 6 h
0.1
1
10
Triamcinolone acet. dose (µg cm-2)

Figure 3

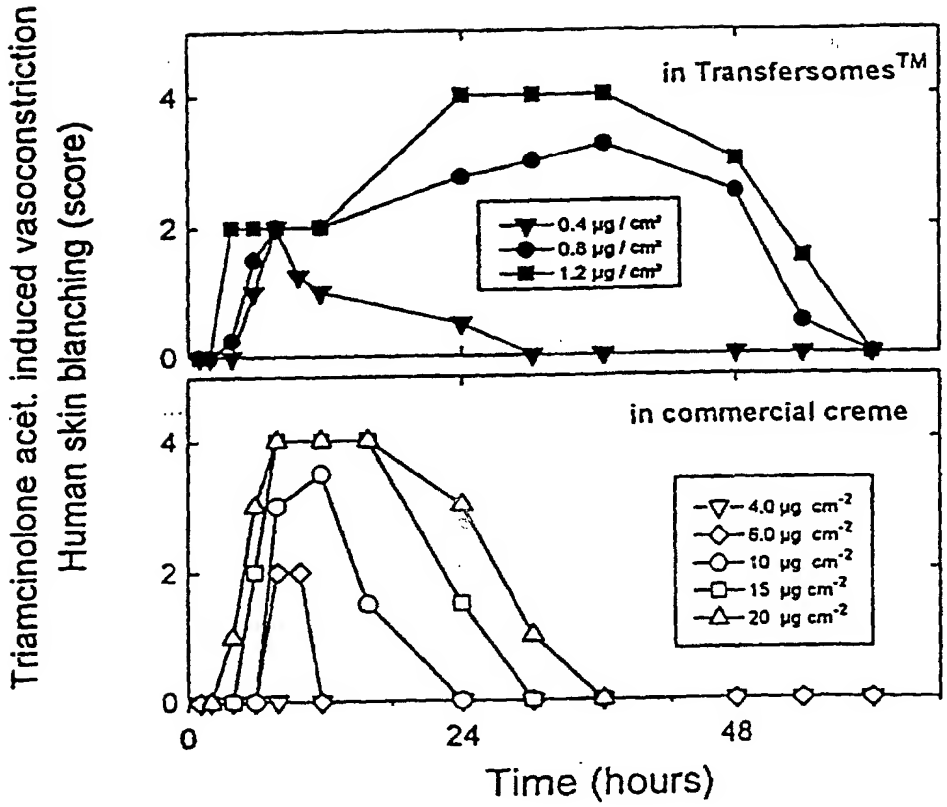

Triamcinolone acet. induced vasoconstriction
Human skin blanching (score)
in Transfersomes™
0.4 µg / cm²
0.8 µg / cm²
1.2 µg / cm²
in commercial creme
4.0 µg cm⁻²
6.0 µg cm⁻²
10 µg cm⁻²
15 µg cm⁻²
20 µg cm⁻²
0
2
4
0
24
48
Time (hours)

Figure 4

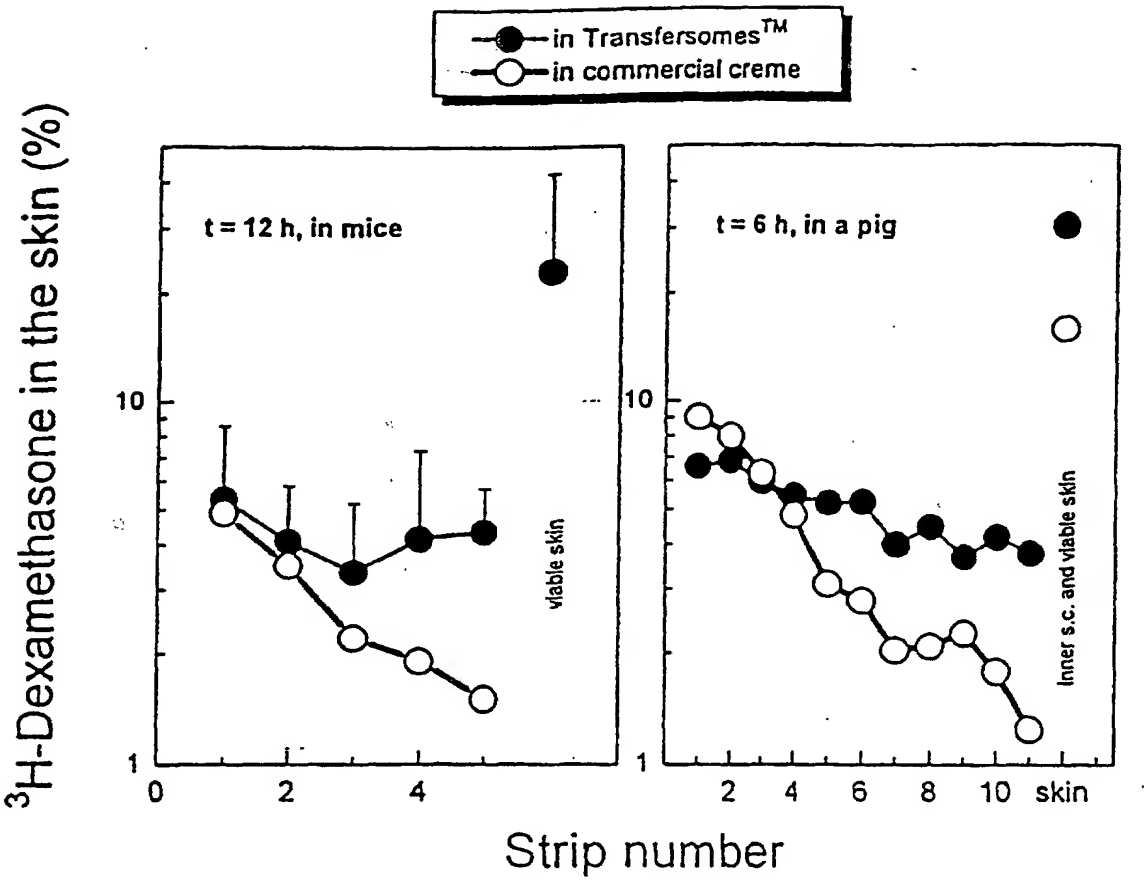

in Transfersomes™
in commercial creme
t = 12 h, in mice
t = 6 h, in a pig
viable skin
Inner s.c. and viable skin
^{3}H-Dexamethasone in the skin (%)
10
1
0
2
4
6
8
skin
Strip number

Figure 5

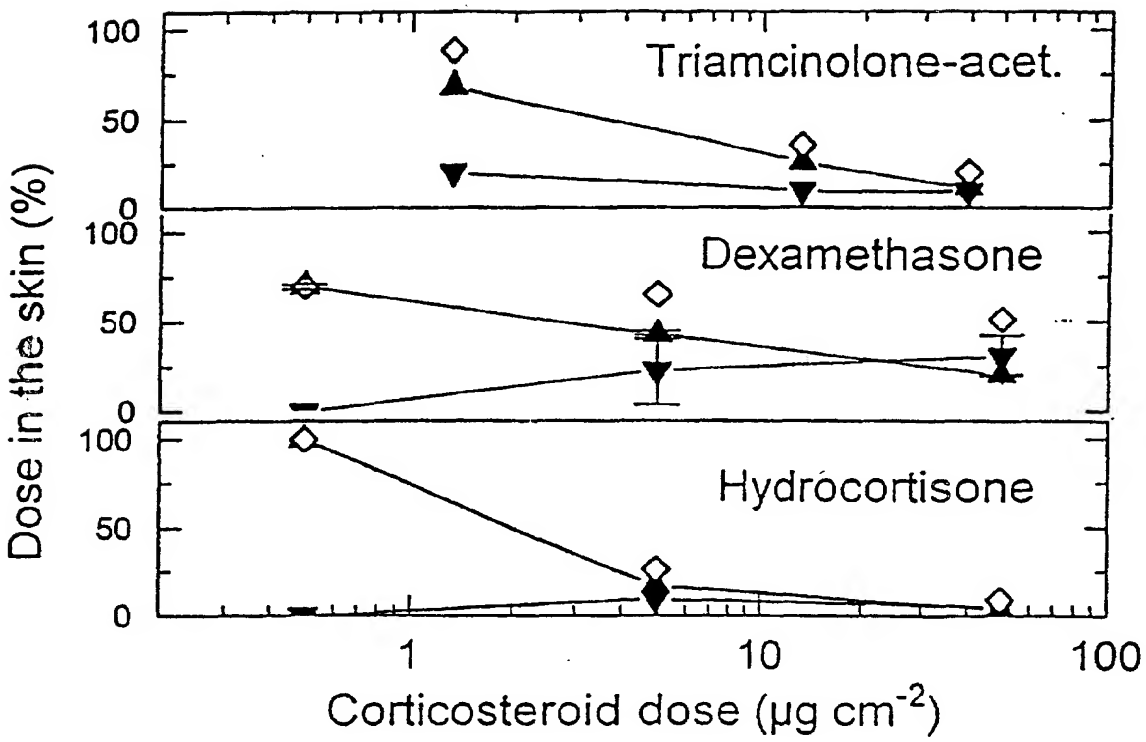

Triamcinolone-acet.
Dexamethasone
Hydrocortisone
Dose in the skin (%)
100
50
0
1
10
100
Corticosteroid dose (µg cm-2)

Figure 6

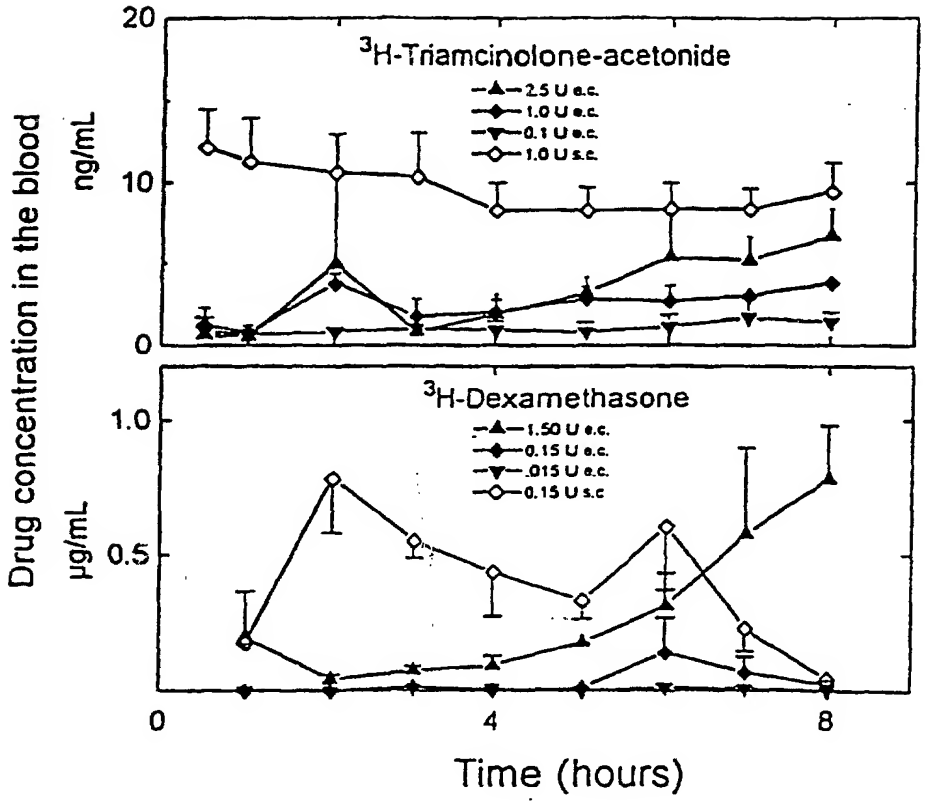

20
10
0
ng/mL
^{3}H-Triamcinolone-acetonide
2.5 U e.c.
1.0 U e.c.
0.1 U e.c.
1.0 U s.c.
1.0
0.5
µg/mL
^{3}H-Dexamethasone
1.50 U e.c.
0.15 U e.c.
.015 U e.c.
0.15 U s.c
0
4
8
Time (hours)
Drug concentration in the blood

Figure 7

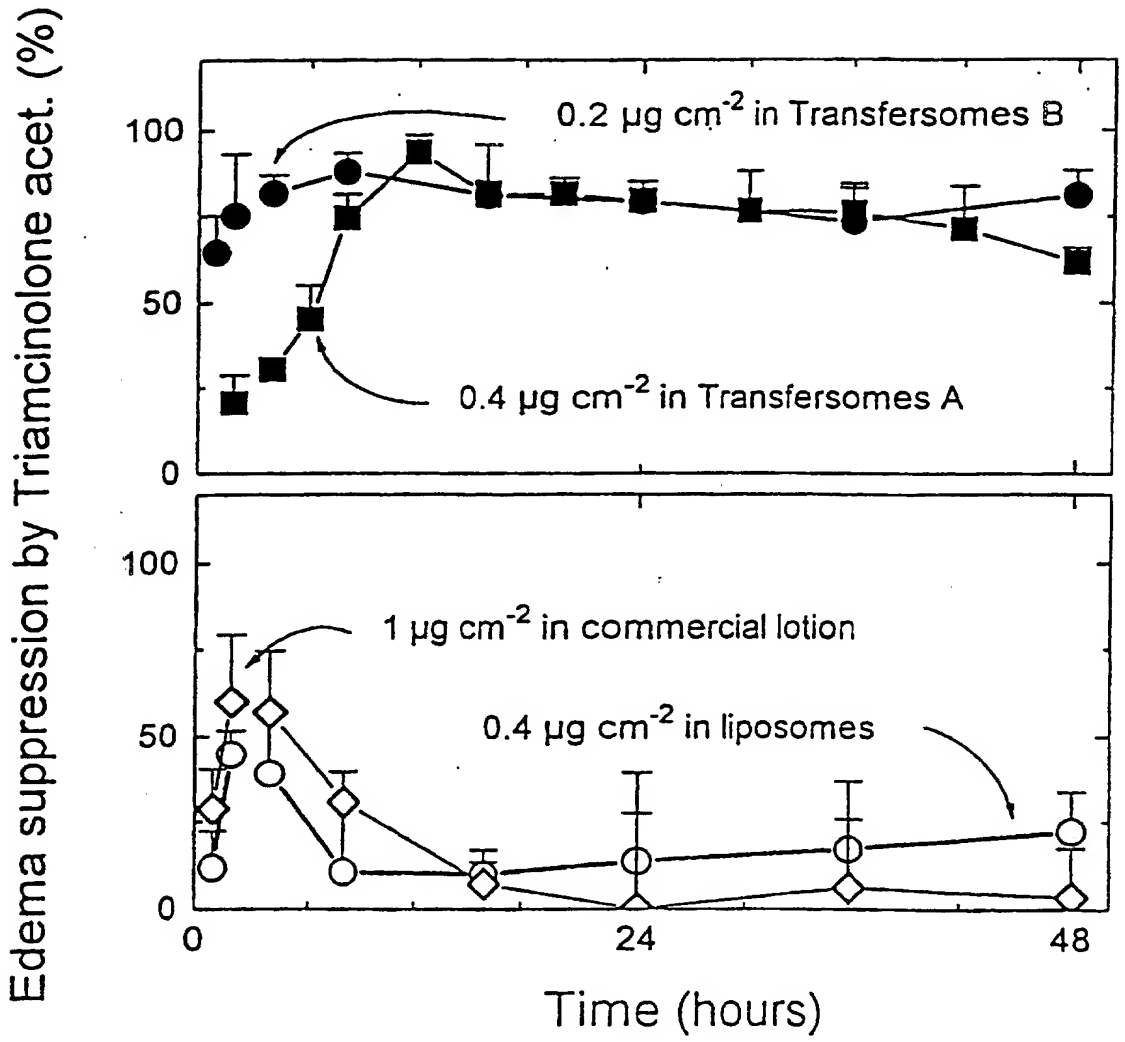

Edema suppression by Triamcinolone acet. (%)
100
50
0
0.2 µg cm-2 in Transfersomes B
0.4 µg cm-2 in Transfersomes A
100
50
0
1 µg cm-2 in commercial lotion
0.4 µg cm-2 in liposomes
0
24
48
Time (hours)

Figure 8